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RESEARCH ARTICLE

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Cerebral oxygen saturation and electrical brain activity before, during, and up to 36 hours after arterial switch procedure in neonates without pre-existing brain damage: its relationship to neurodevelopmental outcome

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Abstract *Objective*: To monitor the pattern of cerebral oxygen saturation (rSat), by use of NIRS, in term infants before, during and after the arterial switch operation and to evaluate its relation to neurodevelopmental outcome. *Methods*: In 20 neonates without pre-existing brain damage hemodynamics and arterial oxygen saturation (AO_2-Sat) were monitored simultaneously with rSat and amplitude-integrated EEG (aEEG) from 4 h to 12 h before up to 36 h after cardiopulmonary bypass (CPB) and short duration of cardiac arrest during deep hypothermia (DHCA). The Bayleys developmental scale was performed at 30 months. *Results*: Before surgery rSat was $<50\%$ in 16 patients. During CPB rSat increased to normal values, with a sharp decrease during brief CA (median 6.5 min). Post-CPB rSat showed a transient decrease (30–45%) despite normal PaO_2 with sustained normalization after 6–26 h. Recovery time of the rSat seemed longer when pre-operative rSat was below 35%, and for lower minimum nasopharyngeal temperature and longer duration of CPB and of DHCA. Recovery time of the aEEG varied and did not correlate with normalization of rSat. Neurodevelopmental outcome was normal in all but two patients. Patients with lower pre-operative rSat ($<35\%$) tended to have lower DQ (developmental quotient) scores at 30–36 months. (median: mental 102 and motor 101 (range 58–125) compared with mental 100 and motor 110 (range 83–125)) *Conclusion*: Despite prompt normalization of circulation and oxygenation after surgery, recovery of rSat of the brain took 6–26 h, probably because of higher energy demand after CPB. Pre-operative cerebral oxygenation may be underestimated as a possible cause of adverse post-operative outcome.

Keywords Newborn · Arterial switch operation · Cerebral oxygenation · Electrical brain activity · Neurodevelopmental outcome

Abbreviations aEEG: Amplitude integrated electroencephalogram · CPB: Cardiopulmonary bypass · CA: Cardiac arrest · DHCA: Circulatory arrest during deep hypothermia · NIRS: Near infrared spectroscopy · rSAT: Regional cerebral oxygen saturation · TGA: Transposition of the great arteries · CVP: Central venous pressure · PaO_2: Arterial oxygen pressure · AO_2-sat: Arterial oxygen saturation · CBV: Cerebral blood volume · DQ: Developmental Quotient

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Introduction

Heart surgery-related brain damage is thought to be related to intraoperative hypoxia and/or ischemia because of disturbances in cerebral perfusion and vasoregulation, in particular during periods of low-flow cardio-pulmonary bypass (CPB) and circulatory arrest during deep hypothermia (DHCA) (Newburger et al.

1993; Ferry 1987; Du Plessis et al. 1995a; van Bel et al. 1996). The clinical signs of secondary brain damage during open-heart surgery are usually delayed recovery of brain perfusion, oxygen metabolism, and electrical brain activity during the rewarming phase, and epileptic activity in the early post-operative period (Du Plessis et al. 1995b; Bellinger et al. 1999, 1995).

On the other hand, there is increasing evidence that adverse neurodevelopmental outcome is often related to brain damage already present before open-heart surgery (Limperpoulos et al. 1999). Most studies, however, investigating perioperative perfusion, oxygenation, and electrical brain activity of the new-born brain are not conclusive about the pre-operative condition of the brain (Greeley et al. 1991; Mezrow et al. 1994; Austin et al. 1997), although severe pre-operative acidosis and hypoxia is mentioned as an important additional risk factor (Hövels-Gürich et al. 2002).

The objective of this study was, therefore, to investigate exclusively the impact of perioperative conditions such as low flow-CPB and DHCA in relation to neurodevelopmental outcome in a homogeneous group of neonates without pre-operative existing brain damage, subjected to open-heart surgery because of transposition of the great arteries (TGA). Cerebral hemodynamics, oxygenation, and electrical brain activity were monitored from 4 h to 12 h before the start of surgery up to 36 h after completion of surgery. Neurodevelopmental outcome was evaluated at 18 months and 30–36 months of age.

Patients and methods

Between January 1998 and June 2000, we were able to collect 20 consecutively admitted term neonates with TGA who had an arterial switch operation. Patient characteristics are listed in Table 1. Infants with pre-existing brain damage, congenital brain abnormalities and/or other (chromosomal) abnormalities were excluded. The Research and Ethical Committee of our hospital approved the study. Written informed consent was obtained from all parents.

Monitoring of cerebral oxygenation by use of near infrared spectroscopy

Transcranial near infrared spectroscopy (NIRS; INVOS 4100; Somanetics, Troy, MI, USA) was used for non-invasive monitoring of cerebral hemodynamics and oxygenation. A self-adhesive transducer containing a light-emitting diode and two distant sensors was fixed on the left parietal side of the neonatal skull. (Wyatt et al. 1986; Edwards et al. 1988) For assessment of cerebral oxygenation fractional cerebral oxygen saturation (rSat) was calculated from the differential signal obtained from these two sensors, expressed as the venous-weighed percent oxygenated hemoglobin (= oxygenated hemoglobin/total hemoglobin [oxygenated hemoglobin + deoxygenated hemoglobin]) (Thavasothy et al. 2002). Changes in cerebral hemodynamics were assessed by measuring changes in cerebral blood volume (ΔCBV) (Pryds et al. 1990).

Monitoring electrical brain activity

An amplitude-integrated continuous electroencephalogram recording (aEEG) cerebral function monitor (CFM 4640, Lectromed Devices, Oxford, UK) was used to monitor electrical brain activity. The CFM records a single channel EEG from two parietal electrodes. The filtered signal is rectified, smoothed, and amplitude integrated. Specifically, different aEEG patterns are looked at by means of pattern recognition—flat tracing (FT), continuous extremely low voltage (CLV), burst-suppression (BS), continuous normal voltage (CNV), and discontinuous normal voltage (DNV). Epileptic activity can also be identified (Helström-Westas and Rosén 1995; Toet et al. 2002). Both the background activity and the presence of seizure activity were taken into account when analyzing the data.

Anesthesia and perfusion techniques

In all patients, anesthesia was induced by use of sevoflurane and oxygen in nitrous oxide ($F_iO_2 = 0.33$). Once an intravenous (iv) line was inserted a switch to total iv anesthesia was made using midazolam and sufentanil; pancuronium was used as neuromuscular relaxant. In 13 patients i.v. lines were already in place and anesthesia was induced intravenously. Ventilator settings were adapted to maintain normocapnia. All patients received dexamethasone (1 mg kg^{-1}). Routine monitoring consisted of EKG, invasive arterial and central venous pressures, pulse oximetry, and central and peripheral temperature measurements. Surface cooling was instituted with low ambient room temperature and a cooling mattress.

An ascending aorta arterial cannula and a single right arterial venous cannula were used. CPB and core cooling started when the cannulae were in place. Flow rates of cooled blood during perfusion are listed in Table 1.

When naso-pharyngeal temperature reached approximately 21°C or lower, low-flow perfusion began. At the end of the CPB, a short period of DHCA was used to close the atrium in 15 patients. In one patient, No 14, the DHCA time was longer, to close the ventricular septum defect. During DHCA, hypothermic temperatures were maintained by surface cooling. Reversal of hypothermia was achieved by perfusion with warmed blood. The acid-base management strategy was pH stat (with correction for body temperature) during cooling and alpha stat (without correction for body temperature) during rewarming in all patients.

Table 1 Important patient characteristics of the 20 newborns subjected to an arterial switch operation because of transposition of the great arteries

Before CPB									During CPB					After CPB			
	Weight (g)	Corvitium	AS	Ventilation	Rashkind	Prostagl.	Inotropes	Max lact	Day after birth	CPB (min)	CA (min)	Minim temp	Flow (mL min^{-1})	Inotropes	Ventilation (h)	Max lact	
1	4,100	TGA, ASD	9	y	–	y	Dopa/adr	27	16	143	9	21	630	Dopa	23	18	
2	2,600	TGA	8/9	–	y	y	Dopa	34	10	145	19	19	532	Dopa/mil	48	23	
3	3,600	TGA	8/8/9	y	y	–	Dopa/mil	25	6	158	7	18	644	Dopa/mil	24	46	
4	3,180	TGA	9	y	y	y	–	12	10	145	7	20	616	Dopa/mil	120	41	
5	2,500	TGA	9	y	–	y	Dopa	16	8	139	4	18	498	Dopa/mil	48	5	
6	4,600	TGA	7/10	–	y	y	–	08	7	130	65	18	728	Dopa/mil	48	38	
7	3,240	TGA PFO/ASD		–	y	y	–		8	135	4	19	616	Dopa/mil	90		
8	3,520	TGA	9/9	y	y	y	–	08	8	145	9	19	644	–	70	15	
9	3,840	TGA, ASD	8/9	y	y	y	–	08	9	138	5	18	672	Dopa/mil/adr	70	37	
10	4,000	TGA		–	y	y	–		9	131	45	175	696	Dopa		39	Tamponade: thoracotomy
11	2,940	TGA	9/9/9	–	y	y	–	29	10	136	53	21	618	Dopa/mil	90	37	Seizure?
12	3,500	TGA	9/10	y	y	y	Dopa	107	10	153	3	17	648	Dopa/mil	70	3	Deterioration 20 h before surgery
13	3,760	TGA, VSD	8/8	y	y	y	Dopa/adr	47	10	139	65	22	643	Dopa/adr/mil	>150	48	Deterioration just before operation/second operation for VSD
14	2,990	TGA/VSD /ASD	9/9	–	–	y	–	14	8	152	24	19	450	Dopa/adr/mil	70	35	Resuscitationafter pericardial puncture
15	3,020	TGA,VSD, PFO	9/10	–	y	–	–	22	40	165	–	25	588	Dopa/mil	40	16	Tamponade: thoracotomy
16	2,955	TGA,PDA, PFO	7/9	y	y	y	Dopa/adr	24	8	138	5	20	587	Dopa/adr/mil	90	26	Bleeding: thoracotomy
17	3,300	TGA	8/9	y	y	y	–	18	7	106	–	21	622	Dopa/mil	70	2	
18	4,040	TGA	9/8	y	y	y	Dopa	15	8	126	–	21	705	Dopa/mil	70	14	
19	3,000	TGA	1/1/5	y	y	y	Dopa/adr	35	8	143	3	215	587	Dopa/mil	130	33	Birth asphyxia/ no signs of hypoxic-ischemia before surgery
20	3,280	TGA	8/10	y	y	y	Dopa/adr	7	125	75	196	644	Dopa/adr	120	16		
Median	3,290		8/9						8	139	65	193	626		70	33	

CPB, cardio pulmonary bypass; TGA; transposition of the great arteries; ASD, atrial septum defect; VSD, ventricular septum defect; PFO, persistent foramen ovale; AS, Apgar score; CA, cardiac arrest; Temp, min lowest nasopharyngeal temperature; Dopa, dopamine; PDA, persistent ductus arteriosis; Mil, milrinone; Adr, adrenaline; Max, lact maximal arterial lactate concentration (mmol L^{-1})

In all but one patient dopamine supplemented by milrinone and/or epinephrine was to wean the patients off CPB. After completion of surgery, patients were transferred to the Pediatric Intensive Care Unit. Artificial ventilation was discontinued when the infants were awake, in a cardiopulmonary stable condition and without or with low doses of inotropic support. Morphine (0.25 mg kg^{-1} day^{-1}) and midazolam (0.2 mg kg^{-1} h^{-1}) were used during the ventilation period for all patients.

Study design

1) Before surgery The rSat of the brain and aEEG, together with arterial oxygen saturation (AO_2-sat), heart rate and blood pressure were recorded for 4–12 h. Cranial ultrasound investigation was always performed to exclude pre-operative brain damage and/or congenital anomalies.

2) During surgery Simultaneous recordings of rSat and aEEG, AO_2-sat, heart rate, blood pressure, nasopharyngeal, rectal and skin temperature, were started and continued throughout the surgical procedure (central venous pressure (CVP), ventilator settings, inspired oxygen and medication were also recorded).

3) Post-surgery After completion of surgery and up to 36 h, simultaneous recordings of rSat, electrical brain activity, AO_2-sat, blood pressure and heart rate were continued for all patients.

4) During the first week post-surgery Cranial ultrasound investigations were performed on days 1, 3, and 7 post-surgery.

Follow-up and neurological evaluation The survivors were evaluated for both motor- and mental development in the follow-up outpatient clinic after 3, 9, 18 months, using the Griffiths mental developmental scale. The Bayleys developmental scale was performed between 30 months and 36 months. (Griffiths 1976; Bayley 1993).

Data collection and analysis

All variables (heart rate, blood pressure, AO_2-sat, venous pressure, body temperatures, rSat, and aEEG) were simultaneously collected, with a frequency of 1 Hz, and stored on a personal computer for off line analysis.

To study overall effects of the operation procedure on the total group we calculated mean values for rSat, AO_2-sat, mean blood pressure and aEEG for each measurement time-point post-operatively.

Our main study goal was then to investigate whether post-operative rSat, as a measure of cerebral oxygenation, was determined by specific patient characteristics or by specific intraoperative procedures. We therefore used all measurements taken during the first 18 h post operatively, which were available for all patients. For repeated measurements analysis of variance (SPSS 9.0) was performed with repeated measurements of post-operative rSat as dependent variable and indicators for above or below median values of possible determinants as independent variables. These determinants were above or below median values of pre-operative rSat (median 35%) as a patient characteristic, and circulatory arrest time (median 6.5 min), minimum nasopharyngeal temperature during CPB (median 19.30°C), duration of CPB (median 139 min) as procedure characteristics (see also Results section).

We tested whether differences between groups in post-operative rSat were constant over time or not (time–group interactions). Absence of statistical time–group interaction was interpreted as a constant difference over time in post-operative rSat between groups with above and below median values of determinants, say, for instance, pre-operative cerebral oxygen saturation below 35% and above 35%. In such cases the mean group difference was provided. For comparison of continuous outcome between groups the Student-*t* test was used. A statistical significance level of $P < 0.05$ was used for all tests.

Results

Pre-surgery blood pressure and heart rate were normal and stable. rSat (normal range: 50–70% (Thavasothy et al. 2002)) and AO_2-sat (normal values >90%) were below the normal range in all but two patients.

After CPB, mean blood pressure, AO_2-sat, and CVP were normal and stable in all patients. Only one patient (patient 15) showed a simultaneous 2 min drop in mean blood pressure and AO_2-sat, due to a cardiac tamponade. This problem was solved immediately and both blood pressure and AO_2-sat recovered instantly.

Table 1 shows the duration of CPB, DHCA, minimal nasopharyngeal temperature, inotropic support, and maximum arterial lactate values. Three patients did not have a circulatory arrest during CPB. The median arrest time in the other patients was 6.5 min. Median duration of CPB was 139 min. Minimal nasopharyngeal temperatures during CPB varied from 17°C to 25°C, with a median temperature of 19.3°C.

Arterial lactate was elevated for a short period only after admission in 13 patients (maximum 8 mmol L^{-1} in one patient), but normalized within a few hours in all infants. One patient (patient 12) had a temporary elevated arterial lactate 12 h before the start of CPB, because of closure of the duct, despite a Rashkind procedure earlier. All patients had normal arterial lactate concentrations before the start of CPB. After CPB the arterial lactate concentrations varied between 1.5 and 5 mmol L^{-1}, but normalized within 1–2 h.

NIRS-determined cerebral regional saturation

The NIRS data of one patient (patient 7) could not be traced because of technical problems. Another patient (patient 17) only had a NIRS recording after the operation. The pattern of the regional cerebral oxygen saturation (rSat) during the entire study period is outlined in Fig. 1.

Before surgery, rSat was stable but below the normal range (50–70%) in all but two patients (range 27–52%; median 35%). Intraoperatively, just before CPB started, rSat dropped simultaneously with blood pressure and AO_2-sat, for 1–3 min in all patients. After CPB was started, rSat increased to normal values (50–70%), with an expected sharp decrease during brief DHCA. Some patients showed a peak of rSat (70–90%) after start of CPB and after completion of cardiac arrest. Post-CPB rSat showed a transient decrease (30–50%) despite normal PaO_2-values. Sustained normalization occurred after 6–26 h in all patients with or without DHCA. Only one patient showed a very short period of decreased rSat (45%) after CPB of only 1–2 h.

Post-operative rSat tended to be lower in those patients with longer duration of CPB ($P=0.07$) and tended to vary with the duration of circulatory arrest. ($P=0.11$). Post-operative rSat was significantly lower in those patients with a lower minimum nasopharyngeal temperature during CPB with an average of 8.3% ($P=0.003$).

However, when we added to the regression model the pre-operative rSat as independent variable, thus adjusting for pre-operative rSat differences between temperature groups, the post-operative rSat still tended to be lower in those patients with lower minimum temperatures, however this difference was no longer significant (7.2%, $P=0.11$).

When comparing those patients ($n=7$) with pre-operative rSat values lower than median (e.g. $\leq 35\%$), post-operative rSat was lower than with pre-operative rSat values above 35% ($n=11$). But this difference was not significant ($P=0.10$; see also Fig. 1, thin black line and hatched line respectively). One patient (patient 20), who was cooled more rapidly during CPB, showed a very short recovery time of rSat, despite low pre-operative rSat (average 29%). When this patient was excluded from the analysis the relationship between lower pre-operative rSat ($<35\%$) and post-operative rSat was significant (9.3 %, $P=0.02$).

NIRS-determined cerebral blood volume

Although the signal producing the values of relative changes in CBV was not optimal because of movement artifacts, it appeared to be rather stable before, during and up to approximately 6–20 h after surgery in all patients.

Pattern of aEEG

Before surgery all infants showed a normal trace (continuous normal voltage with or without sleep-wake cycling). During hypothermic CPB the aEEG showed a flat trace. After rewarming (nasopharyngeal temperature above 35°C), recovery of the aEEG above 5 μV (discontinuous normal voltage pattern) ranged from 0 min to 635 min (10 h and 35 min) with a median of 30 min. However recovery to continuous normal voltage with sleep-wake cycling took much longer, and varied between 8 h and several days. Epileptic activity was not seen in any patient. In one patient there were doubts

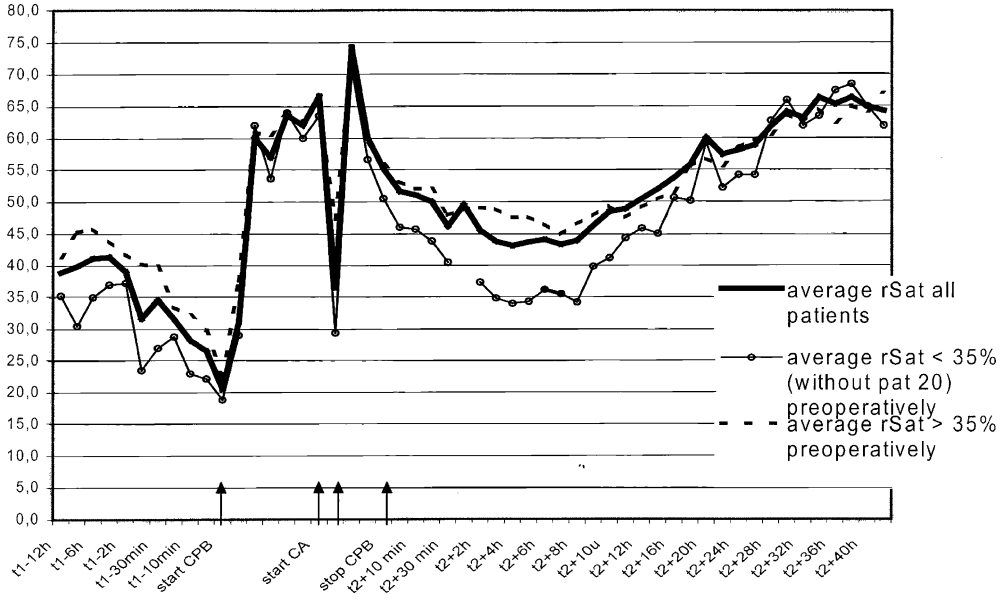

Fig. 1 Cerebral oxygen saturation (%) of the brain perioperatively in 18 neonates subjected to an arterial switch operation. (*t1*, time before CPB; *t2*, time after CPB; ↑1, start CPB; ↑2, start cardiac arrest; ↑3, stop cardiac arrest; ↑4, stop CPB)

about clinical seizures for a very short period. This patient received phenobarbitone. However this could not be confirmed on the aEEG trace.

Recovery time of the aEEG (above 5 μV or regaining continuous normal voltage with sleep-wake cycling) after CPB did not correlate with normalization of the rSat post-operatively. There was no difference in recovery time of the aEEG between the two groups of patients with either a low (< 35%) rSat before surgery versus a higher rSat (> 35%) (Toet et al. 2002).

Cranial ultrasound and magnetic resonance imaging

In all patients except patient 10 cranial ultrasound investigations were performed before, and at day 1, 3, and 7 post-surgery. Except for a plexus cyst in one patient and a broad interhemispheric fissure in another one, no abnormalities were found. Six patients showed increased echogenicity of the periventricular and subcortical white matter during the first few days after surgery, but these echogenicities resolved in four patients. In one patient, in whom the echogenicity persisted for one week, magnetic resonance imaging (MRI) was performed which did not show any signal intensity.

Neurodevelopmental outcome

The age at follow-up ranged from 30 months to 36 months. Results from the Bayley scales at 30–36 months were comparable with the results of the Griffiths scales at 18 months. Neurodevelopmental outcome showed a MDI-Bayley > 80 for all but two of the children. DQs of all patients are listed in Table 2. Although the DQ-scores of patients who had low preoperative rSat values of the brain (≤ 35 %) tended to be lower, this difference was not significant.

Patient 12 had a low DQ (58) at 30 months of age. pre-operatively he was stable up to 12 h before surgery. Then he deteriorated with low arterial saturation, because of closure of the duct with a temporary elevated arterial lactate. All conditions were normal before the start of surgery except for the rSat, which remained below 35%. The post-operative period was uneventful. A MRI scan at 32 months showed no abnormalities, especially no signs of gliosis or atrophy (see also above).

Patient 14 had a low DQ (55), with autistic behavior and a slight motor delay. Cranial ultrasound investigation showed signs of atrophy. MRI at the age 18 months showed atrophy and gliosis as a sign of hypoxic ischemia in the neonatal period. This patient had a low preoperative cerebral oxygenation (rSat < 35) the longest DHCA time (25 min), and needed cardiac resuscitation and a thoracothomy after a pericardial puncture a few weeks after surgery.

Discussion

Eighteen out of 20 neonates had a normal neurodevelopmental outcome at 30 months of age, despite low flow-CPB and brief DHCA intraoperatively, which are thought to be risk factors for perioperative brain damage. (Newburger et al. 1993; Ferry 1987; Bellinger et al. 1999) Both infants with an abnormal neurodevelopmental outcome (patients 12 and 14) had low rSat values (≤ 35) before surgery. The adverse outcome of patient 14 was probably not related to the initial open-heart surgery but to hypoxic–ischemic brain damage during heart failure requiring resuscitation and a re-thoracotomy several weeks after the open-heart surgery.

Despite the fact that adverse neurodevelopmental outcome, psychiatric problems, speech impairment and even motor deficits are reported frequently after arterial switch procedures in neonates and infants and related to

Table 2 Developmental quotient (DQ-scores) of the 20 patients at 30–36 months, subjected to an arterial switch operation, divided by rSat ≤ 35% and > 35%

rSat ≤ 35% before CPB				rSat > 35% before CPB			
	Griffith	Bayley MDI	Bayley PDI		Griffith	Bayley MDI	Bayley PDI
Patient 1		108	110	Patient 2	110		
Patient 3		101	101	Patient 4		102	108
Patient 6		116	125	Patient 5		125	110
Patient 8	100			Patient 9		93	85
Patient 12		58	58	Patient 10		83	93
Patient 14[a]		80	80	Patient 11		118	115
Patient 20		84	84	Patient 13		117	118
				Patient 15		81	94
				Patient 16		93	117
				Patient 18		100	117
				Patient 19	92		
Mean		97	95			101	106
Median		102	101			100	110

[a]Not in calculation

Patients 7 and 17 (no NIRS before operation): Bayley 110/ 111 and 104/ 92, respectively

intraoperative perturbations such as duration of CPB or CA. (Bellinger et al. 1999, 1995; Hövels-Gürich et al 2002; Stieh et al. 1999; Alden et al. 1998; Clancy et al. 2003) the present study supports the notion that lack of pre-operative brain damage may be an important pre-requisite for normal neurodevelopmental outcome after open-heart surgery (Limperpoulos et al 1999), and not intraoperative perturbations per se. However, we must keep in mind that we investigated only a small group of patients with a brief DHCA versus a more prolonged DHCA in other studies. We also realize that cranial ultrasound can only in part exclude brain damage, as do monitoring techniques like aEEG and NIRS. (Toet et al. 1999, 2002; Naulaers et al. 2003).

Contrary to the intraoperative period, in which all patients showed rSat-values in the normal range, they showed an abnormally low rSat (< 50 %) after cessation of CPB and up to about 26 h (mean 12 h) post-surgery, despite normal arterial oxygenation, blood pressures and CVP during this period of time. We can only speculate about the reason of this phenomenon. Because cerebral blood volume (CBV) and therefore total Hb (no changes in hematocrit and/or pump function of the heart were detected during this period) remained quite stable, it is suggested that rSat was lowered mainly as a result of a drop in HbO_2. NIRS measures tissue oxygenation index (TOI) (Naulaers et al. 2003). Although NIRS does not measure oxygen utilization directly, it may point to a higher O_2-utilization by the brain during this early post-surgery period. Earlier studies support this assumption. (Nollert et al. 1998; Kurt et al. 1995; Nomura et al. 1996) Personen et al. (1999) found a lower venous saturation of hemoglobin up to 6 h after DHCA in association with an altered energy status of the brain. Du Plessis et al.(1995a) and Wardle et al. (1998) mentioned in their NIRS studies in infants subjected to open-heart surgery that concomitant changes in total hemoglobin and deoxygenated hemoglobin after cessation of CPB suggested increased cerebral oxygen extraction. Finally Greeley et al. (1991) reported an increased cerebral metabolic rate of oxygen after CPB in those patients who were cooled during CPB to 18°C. It was postulated that this represents a metabolic response to hypothermia, implying restoration from oxygen debt or a forced response to accelerated brain rewarming after cessation of CPB. This phenomenon might explain our finding that patients with lower minimal intraoperative nasopharyngeal temperatures had also lower rSat values during the post-surgery period.

It was intriguing to find that those individuals with lower pre-operative oxygenation levels of the brain, as indicated by rSat values below the median of 35%, had significantly (when excluding patient 20) lower post-CPB rSat values up to 26 h post-surgery. Because CBV was stable in both subgroups, this may indicate that a possible oxygen deficit before surgery gives rise to a higher O_2-utilization in the early post-surgery period. In this respect we must stress that arterial lactate levels before surgery were normal and not different among those individuals with rSat values below and above 35%, which do not support oxygen shortage in any patient. Nonetheless, it may be another indication that pre-operative condition has its impact on the post-surgery energy status of the brain. Pre-operative cerebral oxygen saturation measured by NIRS was indeed found to be critical below 35% and that pre-operative oxygenation might have influenced the response to allopurinol as a neuro-protective agent. (Kurt et al. 1999; Clancy et al. 2001).

It was stated that a ''critical cerebral oxygenation'' (rSatIn this study a variable but uneventful recovery of electrical brain activity after cessation of CPB was seen, as indicated by the patterns of the aEEG in all patients. Also no epileptic activity was detected in any of the infants. Furthermore we did not detect any relationship with important intraoperative factors like duration of low flow-CPB, duration of DHCA, or minimal nasopharyngeal temperature. Newburger et al, reported substantial EEG abnormalities such as ictal activity in the first 48 h after open-heart surgery.

In this study, infants operated under DHCA showed significantly more occurrence of epileptiform activity and a prolonged time to the first reappearance of EEG-activity post-CPB compared with patients operated under low-flow CPB. In this study a relatively large number of infants had neurological abnormalities before surgery, further suggesting that pre-existing brain damage is related to adverse neurodevelopmental outcome. Clancy et al. concluded in a recently published study, that the risk of seizures after DHCA was associated with specific types of congenital heart disease (aortic arch obstruction), the presence of genetic conditions and prolonged DHCA time ($\geq = 60$ min). Although duration of DHCA in our study was very short (median arrest time 65 min), recovery of the post-operative rSat tended to be longer with longer arrest times.

The neurodevelopmental outcome at 30–36 months of age seemed to be normal in 18 out of 20 patients, The DQ-score of patients who had lower pre-operative oxygenation levels of the brain (rSat $\leq$ 35%) seems less favorable (Table 2), although this did not reach significance. Neurodevelopmental outcome can also be influenced by post-operative factors. One patient with an abnormal outcome (patient 14) and signs of cerebral atrophy and gliosis on MRI, needed cardiac resuscitation and a re-thoracotomy several weeks after the initial open-heart surgery for repair of the TGA. It is most probable that this complication, and not the arterial switch procedure, caused the brain damage.

In summary, despite prompt normalized circulation and oxygenation after the arterial-switch procedure, recovery of the rSat of the brain took 2–26 h, probably because of higher energy demand after CPB, hypothermia, with or without DHCA. Recovery time of the rSat tends to be longer with pre-operative rSat values below 35%, lower minimal nasopharyngeal temperature during CPB, longer duration of CPB, and longer duration of DHCA. This suggests that during this post-operative

period, the brain is particularly vulnerable to circulatory and oxygenation disturbances. NIRS may be useful pre-operatively to identify infants at risk of cerebral hypoxic-ischemia, to guide the timing of surgery. We suggest that the pre-operative neurological condition of neonates subjected to this type of open-heart surgery may be underestimated as a possible cause of abnormal neurodevelopmental outcome.

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