Neurological Impact of Slower Rewarming during Bypass Surgery in Infants

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Abstract

Background Hypothermia is a neuroprotective strategy during cardiopulmonary bypass. Rewarming entailing a rapid rise in cerebral metabolism might lead to secondary neurological sequelae. In this pilot study, we aimed to validate the hypothesis that a slower rewarming rate would lower the risk of cerebral hypoxia and seizures in infants.

Methods This is a prospective, clinical, single-center study. Infants undergoing cardiac surgery in hypothermia were rewarmed either according to the standard ($+1$°C in <5 minutes) or a slow ($+1$°C in >5–8 minutes) rewarming strategy. We monitored electrocortical activity via amplitude-integrated electroencephalography (aEEG) and cerebral oxygenation by near-infrared spectroscopy during and after surgery.

Results Fifteen children in the standard rewarming group (age: 13 days [5–251]) were cooled down to 26.6°C (17.2–29.8) and compared with 17 children in the slow-rewarming group (age: 9 days [4–365]) with a minimal temperature of 25.7°C (20.1–31.4). All neonates in both groups ($n = 19$) exhibited suppressed patterns compared with 28% of the infants >28 days ($p < 0.05$). During rewarming, only 26% of the children in the slow-rewarming group revealed suppressed aEEG traces (vs. 41%; $p = 0.28$). Cerebral oxygenation increased by a median of 3.5% in the slow-rewarming group versus 1.5% in the standard group ($p = 0.9$). Our slow-rewarming group revealed no aEEG evidence of any postoperative seizures (0 vs. 20%).

Conclusion These results might indicate that a slower rewarming rate after hypothermia causes less suppression of electrocortical activity and higher cerebral oxygenation during rewarming, which may imply a reduced risk of postoperative seizures.

Keywords
- cardiopulmonary bypass
- neurology/ neurological
- hypothermia/ circulatory arrest
- pediatric
- ischemia/ reperfusion

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Introduction

Therapeutic hypothermia is standard practice during pediatric open-heart surgery to reduce cerebral metabolism and oxygen consumption and thus increase tissue tolerance of a temporarily poor oxygen supply, with the aim of neuroprotection. From animal studies, we know that hypothermia reduces cerebral metabolism by approximately 5 to 10% per °C cooling and, therefore, decreases the oxygen demand in neurons.[1] Although deep hypothermic cardiac arrest (DHCA) is an older organ protection technique, it remains indispensable in certain types of cardiac surgical procedures such as aortic arch reconstruction. Nowadays, selective cerebral perfusion (SCP) is the most widespread technique for neuroprotection.[2,3] Intraoperative hypoxia and other critical events trigger impaired outcomes.[4] Cerebral hypoperfusion is known to carry the highest risk during cooling and the subsequent rewarming phase during cardiopulmonary bypass (CPB).[5] There are different cooling and rewarming techniques, and protocols are not uniform, varying from center to center. Other surgical disciplines already have standardized rewarming protocols, e.g., after asphyxia or resuscitation, with rewarming periods extending up to 3 days.[6]

Relying on these guidelines, in this study, we tried to evaluate the rewarming speed's impact on cerebral oxygenation and electrocortical activity. Our infants with congenital heart defects were rewarmed following an in-house standard or a modified slow-rewarming strategy after deep hypothermic CPB. Simultaneous extended neuromonitoring was performed using near-infrared spectroscopy (NIRS) and amplitude-integrated electroencephalography (aEEG).

NIRS serves to monitor the potential imbalance of oxygen supply and consumption as well as hypoxic events. Rising cerebral metabolic rates and decreased oxygen saturation have been reported during cardiac bypass surgery. Findings like this during intraoperative phases might indicate, i.e., the oxygen supply's adequacy during antegrade SCP.[7]

The aEEG as a diagnostic tool enables reliable interpretation of electrocortical activity.

Considering that anesthetic drugs suppress the clinical symptoms of seizures and that neonatal seizures are usually subclinical, aEEG provides additional information.

Suppressed aEEG patterns and seizures tend to be more common in the neonatal brain.[8] Age-dependent electrocortical reactions are known to occur during events like hypothermia or anesthesia.[9] The brain's immaturity is considered a reason for this phenomenon.[10] A correlation between depressed electrical brain activity and an adverse neurological outcome has been described in children with complex congenital heart disease (CHD).[11]

Both methods represent easy means of continuous, noninvasive, real-time bedside neuromonitoring, and providing attending physicians with valuable information might help to rapidly detect situations carrying a high risk for neurological injury and low cardiac output.[12]

Materials and Methods

Patients

We examined a series of infants (<1 year of age) who underwent cardiac surgery for congenital heart defects via CPB in our tertiary center between April 2014 and August 2017. Inclusion criteria were an age under 12 months and the need for CPB with intraoperative hypothermia below 33°C. Exclusion criteria were the absence of parental consent to participate in the study as well as any suspicion of a syndromic disease (i.e., trisomy 21, DiGeorge) or the evidence of cerebral malformations in cerebral sonography or neonatal seizures diagnosed before surgery. Our local ethics committee approved the study; the application number was 452/14. Children were then chronologically assigned to either the control group undergoing the standard rewarming protocol after cooling, or to a slow-rewarming group as described in detail below.

To facilitate analysis, we estimated the complexity of the congenital heart defect according to the basic EACTS (European Association for Cardio-Thoracic Surgery) mortality score, classifying diagnoses combined with performed procedures in five categories (1 = atrial septal defect/ventricular septal defect correction, 5 = Norwood procedure).[13]

Anesthesia

Anesthesia was induced in all patients with midazolam, sufentanil, and pancuronium. Inhaled sevoflurane and continuous infusion of midazolam and sufentanil ensured maintained anesthesia. Midazolam and sufentanil were administered postoperatively until recovery and weaning from ventilation. Our routine monitoring consisted of central venous and arterial lines. Arterial blood pressure was monitored by an arterial line in the radial or femoral artery.

Extracorporeal Circulation

CPB took place with the mast-mounted Stockert SIII heart–lung machine (Sorin Group, Mirandola, Italy) with customized tubing set in combination with the oxygenator Dideco D100 (Sorin Group Deutschland GmbH, München, Germany) and an arterial filter D130 (Sorin Group, Mirandola, Italy). We maintained a cardiac index of 3.0 L/min/sqm during normothermia in all patients. Intermittent Buckberg's blood cardioplegia was infused for myocardial protection. Hematocrit was kept over a range of 20% and pH was managed according to the α-stat principle. Blood gas was measured at 20-minute intervals. Continuous invasive blood gas monitoring was also established with the Terumo CDI500 (Terumo Corporation, Tokyo, Japan). Perfusion pressure was recorded continuously. Depending on the surgery's complexity and duration, the patient's temperature was cooled down and adjusted using the Stockert 3T Heater Cooler Device (Sorin Group, Mirandola, Italy). The corporal core temperature was measured continuously via a rectal sonde, providing data every 20 seconds. The surgeon performed surgery in DHCA according to the location and complexity of the cardiac defect. For antegrade SCP, an additional arterial cannula was

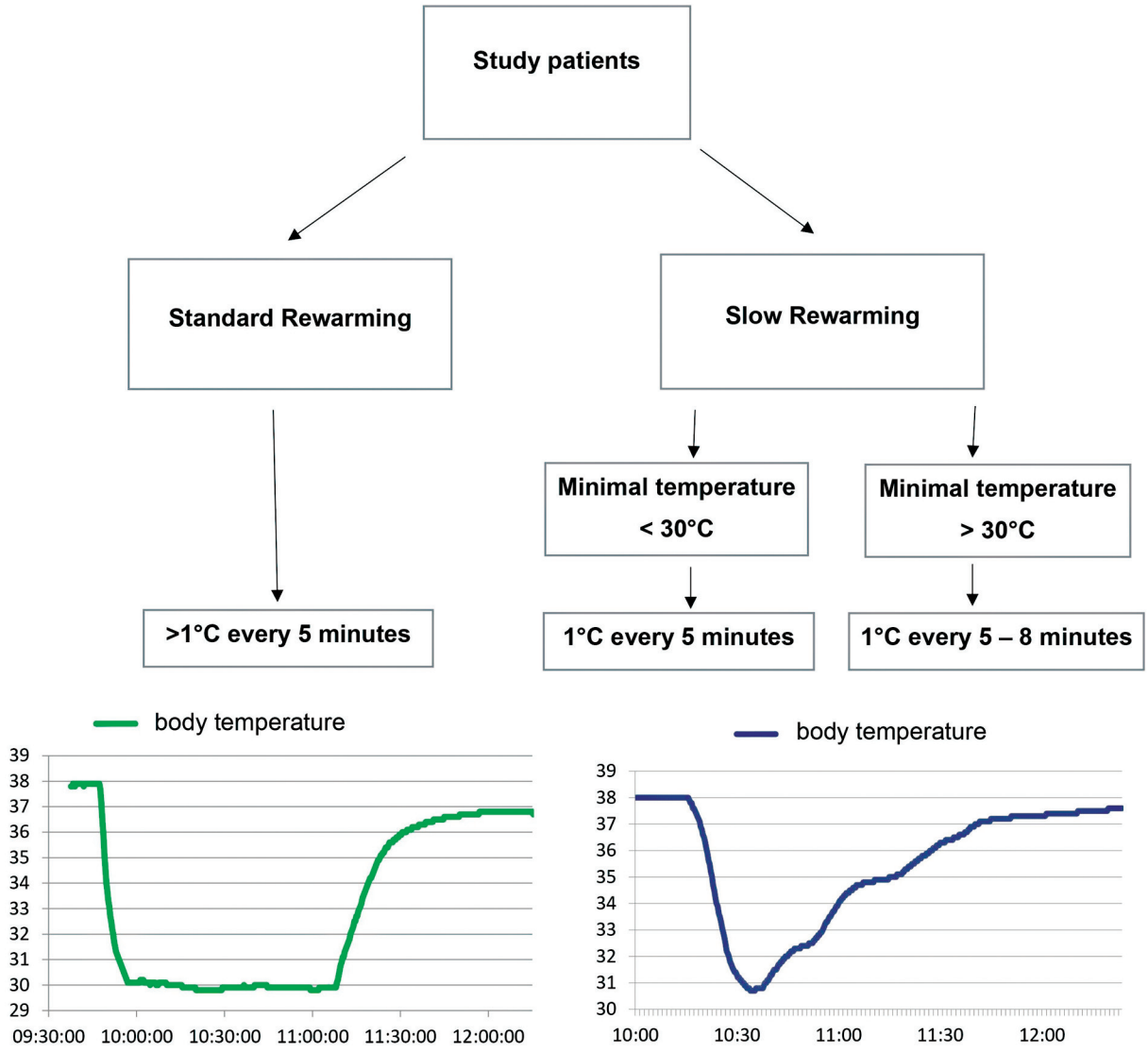

Fig. 1 Flowchart with intraoperative rewarming protocol: division of our study patients into two groups, standard and slow-rewarming group. Slow-rewarming group with variable rewarming rate depending on minimal intraoperative temperature. Illustration of rewarming curve is shown at the bottom of the figure.

introduced into either the carotid artery or to distal end of a modified Blalock–Taussig Shunt.

Our study protocol was developed by an interdisciplinary team to determine two different rewarming rates. The first group, our control cohort, was rewarmed at a relatively quick rate, namely +1°C in less than 5 minutes. To prevent prolonging the duration of CPB, slower rewarming was done according to the depth of hypothermia, meaning + 1°C in 5 to 8 minutes. Our rewarming strategy is illustrated in ►**Fig. 1**.

Aortic reconstruction and diagnosis of total anomalous pulmonary venous connection were major indications for employing DHCA. If weaning from the CPB was impossible without an excessive demand for catecholamines like adrenaline or noradrenaline (>0.3–0.5 µg/kg/min), extracorporeal life support (ECLS) was implanted to facilitate myocardial recovery. In case of any relevant postoperative myocardial edema, sternal closure was delayed.

Postoperative temperatures were measured with a rectal thermometer every 1 or 2 hours, as we were trying to prevent postoperative hyperthermia (>38.5°C). In case of hypothermia, a baby warming unit was established with an individual warming temperature to reach physiological body core temperatures of 35 to 37°C. In case of fever, an external cooling was set up as needed (cold infusions, cooling pillows, cooling mat). Postoperative resuscitation temperature management was individually determined according to internal standards entailing either moderate hypothermia 32 to 34°C or normothermia 35 to 37°C. Accurate management was ensured by ECLS.

Neurological Monitoring

NIRS measured regional cerebral oxygenation in the frontal neocortex ($CrSO_2$) of both hemispheres continuously via two self-adhesive optodes placed on the forehead (►**Fig. 2**). The

Fig. 2 Example of combined neuromonitoring with noninvasive continuous measurements of cerebral oxygenation via NIRS (two optodes on the infants' forehead) and of electrocortical activity deduced from aEEG electrodes (one self-adhesive reference electrode, two-needle electrodes on each hemisphere, fixed with white tape). Also, note the breathing tube and infusion line for venous access. aEEG, amplitude-integrated electroencephalography; NIRS, near-infrared spectroscopy.

principles of NIRS were described previously. We used the (INVOS 5100c Oximeter Somanetics, Medtronic, Minneapolis, Minnesota, United States), which measured $CrSO_2$ at a sample rate of every 20 seconds. Cerebral desaturation was defined as a drop in $CrSO_2$ to values under 55% for longer than 5 minutes.

aEEG continuously measured electrocortical activity via the Olympic Brain Monitor BRM-3 (MedCare Visions, Unterschleißheim/München, Germany). This monitor applied a computer-generated algorithm to filter and compress raw data for each cerebral hemisphere. Data were considered acceptable for analysis according to the following criteria: impedance of under 10 kΩ, absence of movement or electrocardiographic artifact on the raw trace, and absence of interference from diathermy or other electrical devices.

With a standardized template, four-needle electrodes were positioned in the C3/P3 on the left and the C4/P4 positions on the right hemisphere of the international 10 to 20 electroencephalography (EEG) system, one self-adhesive reference electrode was placed on the child's forehead (►**Fig. 2**). This two-channel EEG yields separate data from each hemisphere. A pediatric neurologist experienced in interpreting aEEGs and blinded to clinical information cross-checked all anonymized aEEG recordings offline. The complete compressed background recording and intraoperative raw traces were assessed. Background patterns were classified according to the dominant pattern into five different types of activity according to Hellström-Westas: continuous normal voltage (CNV), discontinuous normal voltage (DNV), burst suppression (BS), continuous low voltage (CLV), and flat trace (FT). We documented the time taken for the aEEG to return to CNV with sleep–wake cycling (SWC) for up to 72 postoperative hours. We defined seizures as repetitive waveforms evolving over a minimum of 10 seconds on either hemisphere. The raw EEG signal was used to confirm suspected seizures on the amplitude-integrated component.

We documented the mean NIRS-derived $CrSO_2$ and the aEEG trace's dominant pattern at each of the predefined phases below:

1. Beginning: time from start of monitoring to initiating CPB.
2. Cooling: start of cooling and maintenance of minimal temperature during hypothermia, possible with either SCP or DHCA.
3. Rewarming: from minimal temperature to core temperature $> 36.0°C$.
4. Weaning: 36.0°C until weaning from CPB/start of ECLS.
5. Ending: time between disconnecting CPB and end of surgery.
6. 6 hours postoperatively.
7. 12 hours postoperatively.

Statistical Analysis

Hemodynamically and neuromonitoring-derived data were collected simultaneously during each phase for each child. For statistical analysis, we used Statistical Package for the Social Sciences (IBM Statistics 20) and Excel (version 15.38). Data were presented with descriptive statistics using median (min–max) for not normally distributed variables. Comparisons were performed with *t*-test for continuous variables, with Mann–Whitney U test for categorical variables and with Fisher's exact test for dichotomous variables. Correlations were calculated with the Spearman's rank correlation. For variance analysis, analysis of variance was performed to

Table 1 Patient diagnoses

Congenital heart defect	*n*	%
d-TGA	11	34
TOF	6	19
Complex SV	4	13
HLHS	4	13
TAPVC	3	9
TAC	2	6
PA	2	6

Note: List of underlying congenital heart defects requiring cardiac surgery.
Abbreviations: d-TGA, d-transposition of the great arteries; HLHS, hypoplastic left heart syndrome; PA, pulmonary atresia; TAC, truncus arteriosus communis; TAPVC, total anomalous pulmonary venous connection; TOF, tetralogy of Fallot; SV, single ventricle (Shone's complex with ALCAPA [anomalous left coronary artery from the pulmonary artery], DORV [double outlet right ventricle] with TAPVC).

identify dependent variables. A p-value < 0.05 was set for statistical significance.

Results

Patients' Characteristics

Thirty-two infants with a median age of 11 (4–365) days, median weight of 3.5 (2.9–8.8) kg underwent cardiac surgery during their first year of life. Twenty-one (65%) infants were male, 18 (56%) were neonates, 97% term infants. Leading diagnoses are listed in ►**Table 1**. Surgical procedures included corrective surgeries (arterial switch operation, aortic reconstruction, complex corrective surgeries with methods like Yasui, Nikaidoh, Rastelli, Colin type 1) as well as palliative surgery (Norwood type 1).

Table 2 Demographic data on patients

Patients	Standard rewarming $n = 15$	Slow rewarming $n = 17$
Age (d)	13 (5–251)	9 (4–365)
Body weight (kg)	3.5 (2.9–7.0)	3.7 (2.9–8.8)
Body length (cm)	51 (46–66)	55 (47–75)

Note: Data are displayed as median (minimum–maximum).

Fifteen children were enrolled in the standard rewarming group and 17 in the slow-rewarming group. Demographic data are presented in ►**Table 2**. There was no significant difference in age at surgery, gestational age, or weight between these two cohorts ($p > 0.49$).

As a matter of fact, rewarming lasted significantly longer in the slow-rewarming group ($p < 0.05$). However, none of the other intra- and postoperative parameters revealed any significant differences, especially total duration of CPB was similar in both cohorts. We detected no significant difference in terms of delayed chest closure, complexity of heart failure, ECLS implantation, or mortality between the control and intervention groups (►**Table 3**). Postoperative hyperthermia (rectal temperature > 38.5°C) occurred in four patients (12.5%) during the first 48 hours after surgery. Intensive care unit (ICU) interventions were external cooling with a mat, administration of paracetamol (PCM), ibuprofen, and metamizole. Four infants underwent resuscitation; two of

Table 3 Perioperative data on both groups

Perioperative data	Standard rewarming $n = 15$	Slow rewarming $n = 17$
Time on CPB (min)	174 (120–354)	197 (87–341)
Minimum temperature (°C)	26.6 (17.2–29.8)	25.7 (20.1–31.4)
Duration of rewarming (min)[a]	33 (21–78)	66 (34–122)
Aortic cross-clamp time (min)	107 (6–241)	108 (56–183)
DHCA (min) [n = number of patients]	15.5 (2–81) [6]	11.5 (2–56) [6]
SCP (min) [n = number of patients]	68 (22–81) [5]	54 (36–56) [3]
Highest lactate intraoperative (mmol/L)	3 (1–9.5)	3.5 (1.5–9.9)
Duration of stay in PCICU (h)	228 (44–480)	183 (21–663)
Time on mechanical ventilation (h)	55 (9–443)	98 (8–444)
Highest lactate postop (mmol/L)	4.8 (2–18)	4.1 (1.3–25)
Delayed closure of chest [n = no. of patients]	6 (2–12) [8]	4 (3–9) [9]
ECLS [n = number of patients]	4 (3–7) [3]	2 (2–2) [1]
Death [n = number of patients]	3	2

Note: Data are displayed as median (minimum–maximum).
Abbreviations: CPB, cardiopulmonary bypass; DHCA, deep hypothermic cardiac arrest; ECLS, extracorporeal life support; PCICU, pediatric cardiac intensive care unit; postop, postoperative; SCP, selective cerebral perfusion.
[a]Difference was statistically significant at $p < 0.05$. [n = number of patients]: as not all patients underwent DHCA or SCP, the actual numbers are displayed in square brackets.

them had an ECLS implanted. One of them was kept hypothermic for 48 hours, three were kept in normothermia.

The aEEG background pattern was suppressed during extracorporeal perfusion to CLV or FT in more than 60% of all children. During optional phases of CPB, namely SCP and DHCA, suppression was detected in 100%. Median $CrSO_2$ values were stable (60–68.5% with the highest median saturation during SCP.

General Observations

All our 19 newborn patients (≤28 days of age) displayed a suppressed aEEG pattern during cooling compared with only 50% of the infants ($n = 7$; $p = 0.02$). Moreover, suppression of aEEG tracing continued in all 19 newborns during rewarming compared with only 28% of the infants ($n = 4$; $p < 0.05$; ►**Fig. 3**). Perioperative seizures occurred in 19% of our patients, all of whom were newborns; seizures were subclinical and thus detected in aEEG; they occurred only during the cooling phase or postoperatively.

We performed cooling to a body temperature of less than 25°C in 12 children. We observed suppressed electrocortical activity at the end of cooling in all of those children (100%), compared with 60% of the 20 children who were cooled down to a body temperature exceeding 25°C ($p < 0.01$). Variance analysis revealed no significant difference between newborns and infants concerning the core temperature ($p = 0.3$). FT was significantly more common in children with higher EACTS Score ($p = 0.001$); $CrSO_2$ revealed no significant change. There was a negative correlation between complexity of heart failure (EACTS Score), minimal core temperature or age ($p < 0.05$), but a positive correlation to duration of CPB ($r = 0.6$, $p = 0.001$).

We measured electrocortical activity during cerebral desaturation ($CrSO_2 < 45\%$ for more than 5 minutes) in 30 patients (93%). Depths of desaturation in combination with aEEG depression varied, but there was no significant correlation. Eight of these patients with a median minimum of 36% (23–51) showed unchanged electrocortical activity; 15 patients with a median minimum $CrSO_2$ of 32% (15–43) revealed a consecutively suppressed aEEG signal (►**Fig. 4**) and seven patients with a median minimum $CrSO_2$ of 37% (18–55) revealed a suppressed aEEG pattern before and during desaturation. Minimal cerebral oxygenation did not differ significantly between those children experiencing contemporaneous electrocortical depression and those who did not ($p = 0.3$). Subgroup analysis between the two cohorts such as DHCA versus no DHCA or ECLS versus no ECLS showed no significant difference in the aEEG pattern, occurrence of seizures, or in cerebral oxygen supply ($p = 0,3$).

Rewarming Strategy

Electrocortical activity was less suppressed during the rewarming phase in the slowly rewarmed cohort; however, the aEEG signal suppression was not statistically significant (►**Table 4**).

We detected postoperative seizures in three children (20%) in the standard rewarming group, whereas no seizure (0%) was detected during the postoperative phase in the slowly rewarmed group ($p = 0.057$). All children revealing seizures in aEEG tracing were newborns.

The median duration to return to CNV with SWC traced in the aEEG was 24 (6–138) hours in children in the standard rewarming group compared with 26 (6–140) hours in those in the slowly rewarmed group ($p = 0.9$).

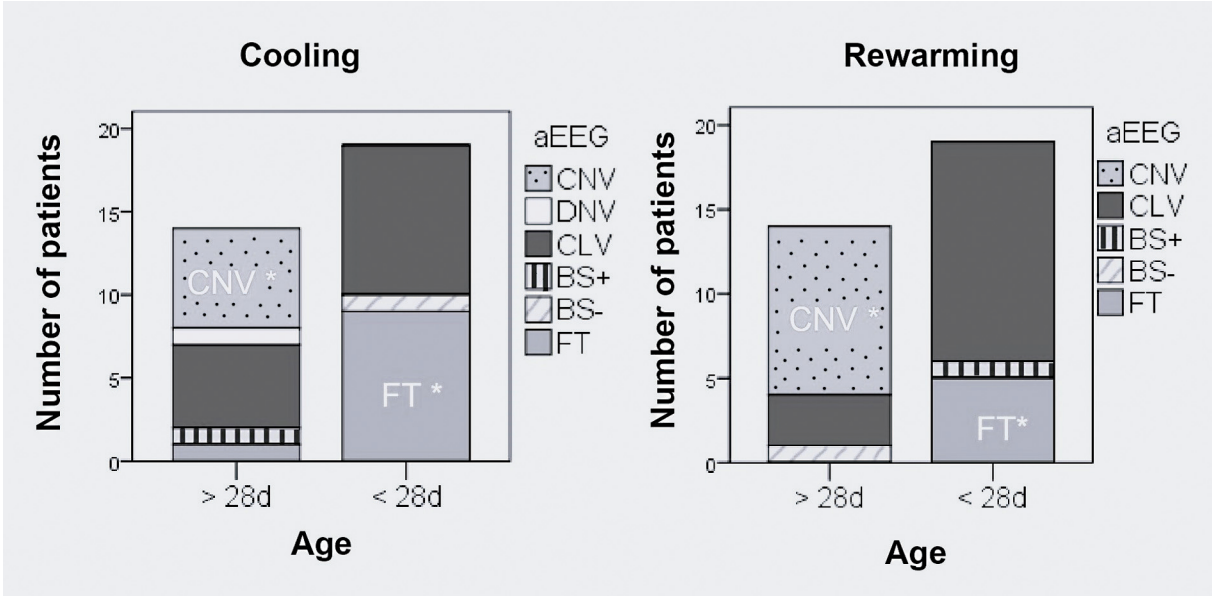

Fig. 3 Bar graph presenting age-dependent aEEG-data during two phases of CPB: aEEG background pattern with suppressed aEEG (CLV, FT) in different shades of gray BS +/− striped, DNV in white, and CNV dotted. On the left, aEEG background pattern during the cooling phase in newborns (<28 days) versus older infants (>28 days). On the right, same bars for rewarming phase. Significant differences in background patterns due to age are labeled with *. aEEG, amplitude-integrated electroencephalography; BS, burst suppression; CLV, continuous low voltage; CNV, continuous normal voltage; CPB, cardiopulmonary bypass; DNV, discontinuous normal voltage; FT, flat trace.

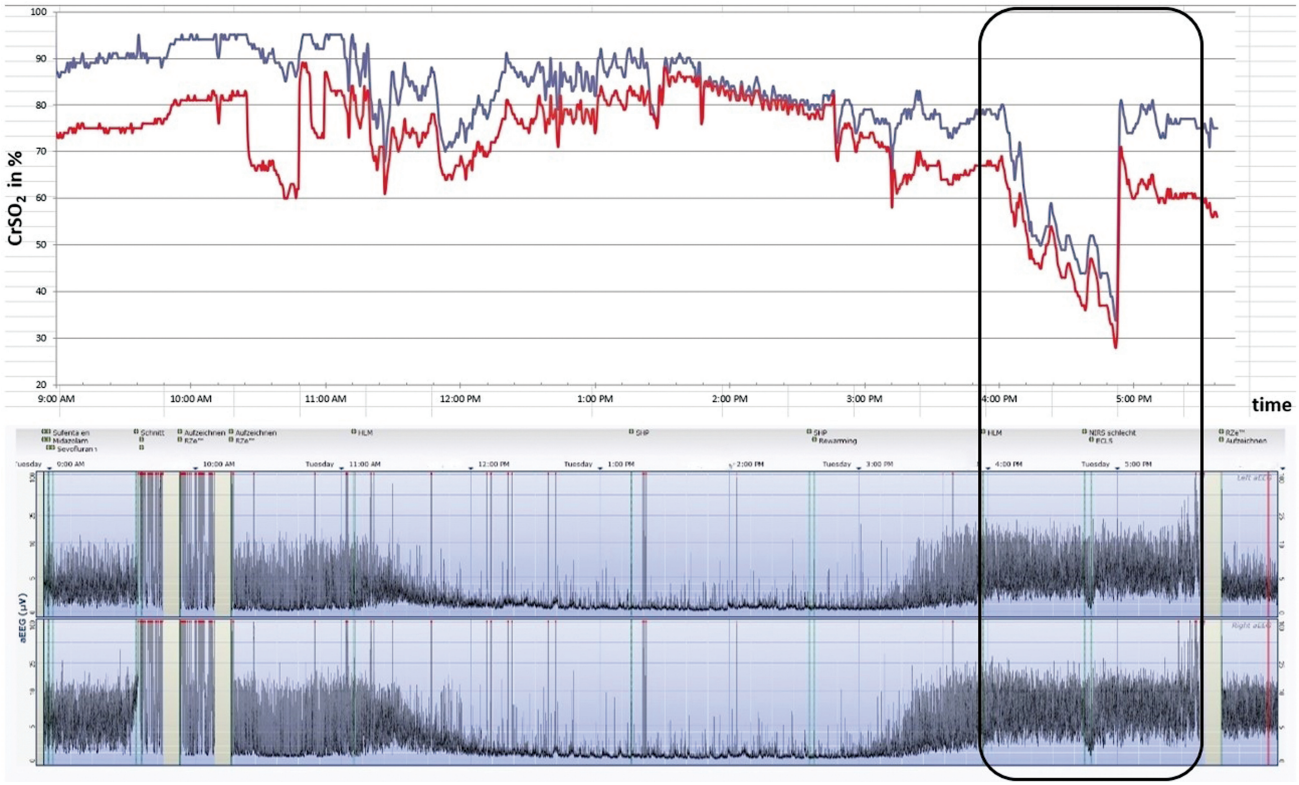

Fig. 4 Cerebral oxygenation (%) is traced above with the left hemisphere displayed by the upper line and the right hemisphere by the bottom line. Simultaneous tracing of electrocortical activity is displayed below with initial discontinuous normal voltage (DNV) tracing after anaesthetization, which was suppressed further to a burst suppression (BS) during cooling down to 25°C. During rewarming, a slow return to DNV was observed, but with a decrease in cerebral oxygenation, which fell below 50% after the attempt to wean from cardiopulmonary bypass in unstable hemodynamic conditions. At 5:00 p.m., cerebral desaturation resulted in a short-term BS. An extracorporeal life support system was implanted followed by immediately improved cerebral oxygenation and a return to DNV.

Table 4 Each group's dominant amplitude-integrated electroencephalography patterns during rewarming are displayed

aEEG pattern during rewarming	Standard rewarming (%)	Slow rewarming (%)	*p*-Value
Normal patterns (CNV/DNV)	26.6	41.2	0.3
Suppressed patterns (FT/BS/CLV)	73.4	58.8	0.3

Abbreviations: aEEG, amplitude-integrated electroencephalography; BS, burst suppression; CLV continuous low voltage; CNV, continuous normal voltage; DNV, discontinuous normal voltage; FT, flat trace.

Cerebral oxygenation reflected by the measured median $CrSO_2$ showed a slightly higher increase by +3,5% during rewarming in the slowly rewarmed group versus + 1.5% in the standard group, but this difference was not statistically significant ($p < 0.939$).

Discussion

In our study involving 32 infants and newborns with complex congenital heart defects, we performed continuous noninvasive neuromonitoring during surgical repair via CPB and intraoperative hypothermia. Simultaneous use of NIRS and aEEG was feasible and might provide important information on cerebral oxygenation and electrocortical activity while facilitating the detection of subclinical seizures.

Our findings in aEEG background patterns are consistent with the literature. There is ample evidence that electrocortical activity is reduced after the administration of anaesthetics[14] and that it is even more significantly depressed during hypothermia,[15] certainly one of the neuroprotective mechanisms to reduce the metabolic demand during phases of reduced or interrupted perfusion and oxygen supply. We administered sufentanil, midazolam, and inhaled sevoflurane in our study. These anesthetics trigger suppressed cerebral activity.[16] In addition, anesthesia influences autoregulatory mechanisms of the brain, thus affecting cerebral oxygenation. The complex interaction of blood pressure, neurovascular coupling, and vasomotor reactivity to maintain cerebral blood flow is affected.[17] Other factors influencing cerebral oxygenation are the hemodynamic status, hemoglobin concentration, and body temperature, all controlled by CPB.[18] Procedure-induced changes in cerebral blood supply must be considered as well. For example, the pulmonary blood steel effect after shunt operations as well as the lower systemic oxygen

saturation in these children do certainly have an impact on the cerebral oxygenation and in a situation with an impaired cerebral autoregulation may be also on electrocortical activity. However, in our study, the performed shunt operations were equally distributed between the two cohorts, and therefore, an impact on the general results should not be expected.

aEEG tracing was depressed to flat trace during cooling, especially in neonates. The fact that seizures occurred only in our study group's neonates together with our observation that their electrocortical activity was significantly more depressed supports the research evidence indicating that the neonatal brain seems to be more vulnerable during CPB and hypothermia.[19] The cerebral reaction to anesthetic drugs also seems to differ depending on gestational age.[9]

Furthermore, we observed significantly lower electrocortical activity in infants cooled to body temperatures beneath 25°C, while median cerebral saturation appeared to be slightly higher. There are similar aEEG findings in the literature consistent with ours regarding hypothermia.[8] A correlation between the depth of hypothermia and oxygen consumption has been well investigated, with hypothermia providing a longer duration of tissue tolerance to less or even no perfusion.[1] One could assume that these results reveal success in meeting the metabolic demands of reduced cerebral metabolism. It might also be reflected by the preserved cerebral oxygenation measured during SCP or hypothermic cardiac arrest, as described in another study.[20] Such simultaneous monitoring revealed the highest levels of median cerebral oxygenation combined with suppressed cerebral activity occurring during SCP, striking why this method has become the preferred approach nowadays.[21]

Children who were slowly rewarmed exhibited a tendency toward less suppressed electrocortical activity during rewarming. At the same time, their cerebral oxygenation rose more than in the standard rewarming group, but neither effect reached statistical significance.

Interestingly, we observed no postoperative seizure in the slowly rewarmed group, a finding that not only stands in contrast with our control group (20%) but also with the incidence reported in the literature.[22] A return to a normal pattern together with SWC traced in the aEEG did not differ between our slowly and rapidly rewarmed groups of children. Gunn et al reported that perioperative seizures were common in their infant cohort, but they did not affect 2-year neurodevelopmental outcomes.[11] As we are all aware, neurological abnormalities can develop and even first appear after 2 years of age or even later.[23] A 4-year neurodevelopmental outcome study in children suffering from complex CHD reported that an abnormal postoperative background pattern and lack of return to SWC are markers for subsequent impaired cognitive development.[24] Postoperatively, hyperthermia should be avoided since it also seems to raise the risk of neurodevelopmental impairment and mortality.[6] Except for this matter, the literature is quite inconsistent concerning temperature management after cardiac surgery or cardiac arrest in children. Retrospective studies as well as randomized controlled trials analyzing hypothermia versus normothermia revealed no difference in mortality or functional outcome.[25,26]

The intraoperative duration of DHCA is an important risk factor for an impaired developmental outcome at 8 years of age.[4] The protective effects of hypothermia during CPB have been questioned since the publication of contradictory evidence.[27] Targeted temperature management favoring normothermia during CPB is accompanied by improved tissue perfusion and briefer intubation, shorter ICU stays, and less need for catecholamines.[28] Despite this evidence, DHCA is reserved for complex surgeries; durations of 30 to 40 minutes are considered to be safe. As longer durations can damage the central nervous system, durations should be minimized. This technique is still being developed and improved by additional methods like SCP.[2] There is unfortunately no consistent intraoperative temperature management guideline for cardiac surgeons correcting CHDs.

Complex diagnoses, age at surgery, and postoperative complications are perioperative variables. New data suggest intellectual impairment and significantly lower IQs, especially in children with more severe cardiac diseases. The same risk constellation has been described regarding the psychological well-being of infants with CHD, as they experience emotional maladjustment and an impaired quality of life.[29]

As our study patients' neurological development has not yet been assessed, we cannot say whether our slower rewarming strategy after hypothermic CPB actually enhances neuroprotection and thus enables a better neurological outcome. We intend to conduct a neurodevelopmental follow-up study in all of this study's surviving patients.

Simultaneous monitoring of electrocortical activity and cerebral oxygenation in our study, especially during desaturation, revealed no clear desaturation threshold at which cerebral activity was suppressed due to a low oxygen supply. Whether temporarily depressed electrocortical activity after desaturation occurred or not did not retrospectively indicate a certain depth of minimal cerebral oxygenation. A Dutch study investigating simultaneous neuromonitoring of pediatric cardiac patients described critical oxygenation as $CrSO_2$ of 30 to 50%.[12] An animal study described cerebral hypoxia–ischemia NIRS thresholds for functional impairment between 33 and 44%, suggesting a buffer between normal and dysfunction.[30] In our study (reassuringly), we probably remained within this buffer zone in most of our children. Cerebral oxygenation is also a product of both the oxygen supply (perfusion and oxygenation) and cerebral oxygen consumption determined by brain metabolism. These factors can be kept in balance by targeted reduction of brain metabolism, together with an adequate oxygen supply. The increased cerebral activity, together with a higher increase in cerebral oxygenation we observed, might indicate the adequacy of this balance in our slow-rewarming strategy group children. This is supported by the fact that we detected no seizures, especially among the neonates who were rewarmed slowly.

Study Limitations

Our interventional cohort study has several limitations that may affect its results. For one, our study cohort (containing

32 infants) is relatively small and heterogeneous because of the broad range of various CHDs included. This limits the validity, especially in subgroup analysis. Second, as prolonging the duration of CPB in total should be avoided, we achieved no consistent rewarming rate. We had to adjust the rewarming rate depending on the intraoperative depth of hypothermia.

Finally, our study patients have not yet undergone neurological reassessment.

We are planning a study providing neurological follow-up data on all surviving patients to actually deliver evidence on possible neuroprotective effects.

Conflict of Interest
None declared.

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