Impact of temperature on the Narcotrend Index during hypothermic cardiopulmonary bypass in children with sevoflurane anesthesia

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Abstract

Background: During cardiopulmonary bypass (CPB) in children, anesthesia maintained by sevoflurane administered via the oxygenator is increasingly common. Anesthetic uptake and requirement may be influenced by the non-physiological conditions during hypothermic CPB. Narcotrend-processed EEG monitoring may, therefore, be useful to guide the administration of sevoflurane during this phase.

Objective: The objective of this prospective, clinical, observational study was to assess the correlation between body temperature, Narcotrend Index (NI) and administered sevoflurane in children during CPB.

Methods: Forty-four children aged 0 to 10 years undergoing hypothermic cardiac surgery were studied. On bypass, anesthesia was maintained with sevoflurane administered via the oxygenator of the heart-lung machine. Nasopharyngeal temperature, NI and minimum alveolar concentration (MAC) of sevoflurane were recorded in intervals of 10 minutes. Expiratory gas was sampled from the oxygenator’s sole expiratory port via a separate connecting line and the MAC was measured by the agent analyzer of the anesthesia machine.

Results: Raw (r = 0.74) and corrected (r = 0.73) r-values show that narcosis depth (as indicated by NI) can primarily be explained by the interaction of MAC and temperature. The analysis of variance (without the interaction term) confirms the significant and independent association of both factors, MAC (p<0.004, 95%CI: 0.19 to 0.46) and temperature (p<0.0001, 95%CI: 0.68 to 0.78), with the NI. During hypothermia, sevoflurane had been reduced significantly (r = 0.41, p<0.0001, 95%CI: 0.33 to 0.48).

Conclusion: Perfusionists and anesthetists should be aware of the results of processed electroencephalograph (EEG) monitoring during CPB. Sevoflurane requirements differ inter-individually; they may decrease during cooling and increase during rewarming. Therefore, it seems reasonable to include the results of processed EEG monitoring when administering sevoflurane during CPB in children, but further studies are necessary to confirm this thesis.

Keywords

EEG; Narcotrend; infants; children; sevoflurane; hypothermia; cardiopulmonary bypass; cardiac surgery

Introduction

During cardiopulmonary bypass (CPB) in children, anesthesia maintained by volatile anesthetics administered into the fresh gas flow line of the oxygenator is increasingly common. This approach requires close cooperation between the attending perfusionists and the anesthetists.

Monitoring the depth of anesthesia is generally desirable for all age groups because patients show an inter-individual variability of responses to anesthetic drugs.
The incidence of intraoperative awareness during cardiac surgery is higher than during other procedures and an overdose may result in cardio-circulatory depression, high-dose vasopressor therapy being required and negative outcome. During CPB, anesthetic uptake and requirement may be influenced by non-physiological conditions. Metabolic rate and cerebral oxygen consumption decrease during hypothermia and can potentially lead to suppression of the EEG. It is known that hypothermia alone already reduces the level of consciousness and can lead to hypnosis. Therefore, we conducted a prospective clinical observational study to assess the correlation between body temperature, Narcotrend Index and administered sevoflurane concentration in infants and children during CPB.

### Methods

This study was conducted according to the standards set forth by the Declaration of Helsinki and Good Clinical Practice guidelines. Following the local ethics committee’s approval (Ethics Committee of Hanover Medical School, Germany, Chairperson Prof. Dr. H. D. Troeger, No. 3259-2016 dated June 22, 2016), 44 children ranging from 0 to 10 years of age scheduled for elective cardiac surgery with CPB were included in this prospective observational study. Children were excluded from this study if they suffered from neurological disease, showed severe developmental delay or if they preoperatively received drugs that altered the EEG (besides pre-medication with midazolam). The study was conducted from September 2016 to March 2017 at the Clinic for Anesthesiology and Intensive Care Medicine, Hanover Medical School, Germany.

Children older than one year of age received oral premedication with midazolam 0.5 mg/kg, given as syrup approximately 45 minutes before arrival at the operation unit. Anesthesia was induced by the injection of 0.5 mg/kg etomidate, 0.5 μg/kg sufentanil and 0.5 mg/kg atracurium followed by tracheal intubation. Thereafter, anesthesia was maintained with sevoflurane adjusted according to the attending anesthetist’s discretion and 1 μg/kg/h sufentanil infusion. Decisions about anesthetic management and the child’s scheduled operation continued, as per usual practice, during data collection.

CPB was performed with the heart-lung machine LivaNova S5 (LivaNova PLC, London, UK) and different oxygenator systems (up to 10 kg: TerumoFX05, Terumo Corporation, Tokyo, Japan; 10-17 kg: Medtronic Pixie, Medtronic GmbH, Meerbusch, Germany; 17-30 kg: LivaNova D101, LivaNova PLC,). The system was prepared in a standardized fashion. The circuit was primed with a bicarbonate-buffered hemofiltration solution (BB-HS; Duosol, B. Braun, Melsungen, Germany) followed by ten minutes circulation. The fluid was hemofiltered using a polysulfone hemofilter (ME HF0S 0020, Medos AG, Stolberg, Germany). After restoring approximately 1000 mL of ultrafiltrate with BB-HS and replacing the pre-bypass filter, 2 mL/kg mannitol, 150 IU/kg of heparin and 20 mL/kg gelatin were added. In infants with a body weight below 5 kg, 10 mL/kg albumin was used instead of gelatin. Packed red blood cells were added, if necessary, to achieve hemoglobin levels of 8-10 g/dL. During CPB, non-pulsatile perfusion was performed. Target pump flow was 2.7 L/min/m² for children and 3.0 L/min/m² for infants below one year of age. Target mean arterial pressure was guided by near-infrared spectroscopy (NIRS) and continuously measured central venous oxygenation in the venous line of the bypass. Arterial CO₂ tension (PaCO₂) was maintained at 35 to 40 mmHg (corrected for temperature, pH-stat) and arterial oxygen tension (PaO₂) at 150 to 200 mmHg.

On bypass, anesthesia was maintained with 1 μg/kg/h sufentanil infusion and sevoflurane administered into the mixed fresh gas flow line of the oxygenator through a sevoflurane vaporizer mounted on the heart-lung machine; the dose was adjusted according to the attending perfusionist’s and anesthetist’s discretion. Expiratory gas was sampled from the oxygenator’s sole expiratory port via a separate connecting line and was measured by the agent analyzer of the Dräger Primus anesthesia machine (Dräger GmbH, Lübeck, Germany). Vasoactive and inotropic drugs were given depending on clinical necessities.

Standard monitoring for all children included electrocardiogram, invasive arterial blood pressure, central venous pressure, pulse oximetry, near-infrared spectroscopy (NIRS), nasopharyngeal and rectal temperature, end-tidal sevoflurane concentration, capnography and urinary output. The EEGs of each patient were recorded continuously with the EEG monitor Narcotrend (Narcotrend Compact M, software version 3.1, MT MonitorTechnik, Bad Bramstedt, Germany). The Narcotrend EEG monitor performs automatic analysis of the electroencephalogram recorded during anesthesia and classifies the EEG automatically. It is approved by the FDA (Food and Drug Administration) and feasible for measuring the anesthetic depth in children during sevoflurane anesthesia. As the EEG changes throughout life, the classification algorithms take the patient’s age into account. The Narcotrend checks the EEG signal during anesthesia with regard to the level of EEG differentiation. If an EEG is differentiated, the monitor uses a scale that consists of stages from A = awake to F = very deep anesthesia (including 15 sub-stages, such as E₀, E₁, E₂, etc.). Additionally, the Narcotrend Index from 100 = awake to 0 = very deep anesthesia is calculated to indicate EEG changes during anesthesia with a finer solution (Table 1).
Narcotrend index (NI), NIRS, nasopharyngeal temperature and minimum alveolar concentration (MAC) of sevoflurane were recorded in intervals of 10 minutes. MAC 1.0 of a volatile anesthetic is the alveolar (or end-expiratory) concentration at which 50% of patients will not show a motor response to a standardized surgical incision. This concentration is higher in infants and lower in the elderly. MAC values are empirical dose-effect data provided by manufacturers and displayed along with Vol% by most modern anesthetic machines. Standard MAC values assume the absence of all other potentially sedative or hypnotic drugs. In combination with opioids (balanced anesthesia), it is common to administer a MAC of 0.8 to 1.0 of a volatile anesthetic for the maintenance of general anesthesia. As children’s MAC depends on age, we used the age-adapted MAC provided by Abbott Laboratories, automatically indicated as multiples by the anesthetic machine, instead of Vol% for data analysis.

All recorded data were analyzed using MS Excel (Excel 2010; Microsoft, Seattle, WA, USA), GraphPad Prism (Prism 7; Graph Pad Software Inc., San Diego, CA, USA) and SPSS 24 (IBM SPSS Statistics for MAC, Version 24.0; Armonk, New York, USA) software tools, and presented as mean values plus standard deviation and 95% confidence intervals. Spearman correlation, regression analysis and independent-samples Mann-Whitney-U tests were performed with a pre-defined significance level of \( \alpha = 0.05 \).

### Results

A total of 44 children were included. Four children below three months had to be excluded because of undifferentiated EEGs resulting in unfrequently indicated NI. Three children received aortic arch repair; data collected during the phase of deep hypothermic circulatory arrest were excluded. Patient characteristics are summarized in Table 2. Types of surgical procedures are summarized in Table 3.

Spearman correlation analysis revealed a significant correlation between nasopharyngeal temperature and NI \((r = 0.74, p<0.0001, 95\%CI: 0.69 \text{ to } 0.77, \text{ Figure 1})\). During hypothermia, MAC of sevoflurane had been slightly, but significantly reduced by the attending perfusionist and anesthetist \((r = 0.41, p<0.0001, 95\%CI: 0.33 \text{ to } 0.48)\). Since a lower temperature results in a lower NI, the overall correlation between NI and MAC became positive during CPB \((r = 0.41, p<0.0001, 95\%CI: 0.33 \text{ to } 0.48)\). Since a lower temperature results in a lower NI, the overall correlation between NI and MAC became positive during CPB \((r = 0.41, p<0.0001, 95\%CI: 0.24 \text{ to } 0.44)\), while normally decreasing doses of volatile anesthetics result in an increase in NI. NI and MAC of sevoflurane at different temperatures during CPB are demonstrated in Table 4. A wide inter-individual variation of NI could be observed. During hypothermia, reduced doses of sevoflurane still resulted in deep anesthesia. MAC groups of sevoflurane and resulting NI at different temperature ranges during cardiopulmonary bypass in children are shown in Figure 2.
Perfusion

According to the SPSS procedure “generalized linear models-univariate”, the NI is significantly influenced by both MAC and temperature as well as the interaction term of both. Raw (r = 0.74) and corrected (r = 0.73) r-values show that narcosis depth (as indicated by NI) can primarily be explained by these two factors. The analysis of variance (without the interaction term) confirms the significant and independent association of both factors MAC (p<0.004, 95%CI: 0.19 to 0.46) and temperature (p<0.0001, 95%CI: 0.68 to 0.78) with the NI.

The near-infrared spectroscopy (NIRS) results showed an increase in NIRS with decreasing nasopharyngeal temperature (r = -0.36, p<0.0001, 95%CI: -0.43 to -0.28) and decreasing NI (r = -0.42, p<0.0001, 95%CI: -0.48 to -0.33).

**Discussion**

Our study showed that, according to the results of processed EEG monitoring, the sevoflurane requirements during cardiopulmonary bypass vary significantly inter-individually, decrease during cooling and increase during rewarming. Therefore, close co-operation of perfusionists and anesthetists is necessary and it seems reasonable to include the results of processed EEG monitoring when administering sevoflurane during CPB in children.

Prediction of individual anesthetic requirements in pediatric cardiac anesthesia is a difficult challenge. During CPB, many factors other than the dose of anesthetic drugs alone can influence anesthetic depth: hypothermia, hemodilution, hypotension and non-pulsatile blood flow can alter drug absorption, distribution, metabolism and elimination, resulting in changes in pharmacokinetics and pharmacodynamics.5

Volatile anesthetics are increasingly used in pediatric cardiac surgery. They decrease the incidence of perioperative awareness, are titratable and measurable via the CPB machine oxygenator12 and, especially in children, facilitate cooling and rewarming during CPB because of their vasodilatory effect. During the beginning and at the end of CPB, special attention should be paid to the fact that sevoflurane may be administered by two vaporizers: one mounted at the CPB machine, administering sevoflurane via the oxygenator and the other at the anesthetic machine, administering sevoflurane along with the ventilation; therefore, close communication is necessary, especially during these phases. At our clinic, we fixed the Narcotrend EEG monitor in a position easily visible to the perfusionist.

Most anesthetists and perfusionists follow the manufacturer’s recommended age-adjusted MAC values, but, generally, age-adjusted MAC values are based on limited data and their accuracy is not clear. It should also be considered that the MAC does not represent inter-individual variability in dose requirements. During CPB, depending on the oxygenator model that is used, measurements of the volatile anesthetic concentration in the oxygenator exhaust may be unreliable for monitoring the administered sevoflurane. For example, the uptake of volatile anesthetics into blood via poly-(4-methyl-1-pentene) (PMP) membrane oxygenators during CPB is severely limited.13 Other factors, such as hypothermia, hemodilution and changes in the oxygenator fresh gas supply flow, can influence sevoflurane plasma concentration.14 Therefore, processed EEG monitoring (e.g., Narcotrend, bispectral index (BIS)) may be beneficial to guide the administration of anesthetics during CPB and may be the only valuable measurement of anesthetic depth.

Several factors may contribute to the increased risk of awareness during cardiac surgery, e.g., altered anesthetic drug pharmacokinetics and dynamics related to CPB and changes in body temperature and masking of

### Table 3. Surgical procedure type (n=44).

<table>
<thead>
<tr>
<th>Procedure</th>
<th>n</th>
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<tbody>
<tr>
<td>Septal defect repair</td>
<td>16</td>
</tr>
<tr>
<td>Valve replace/repair</td>
<td>10</td>
</tr>
<tr>
<td>TOF repair</td>
<td>4</td>
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<tr>
<td>Glenn-anastomosis</td>
<td>4</td>
</tr>
<tr>
<td>AV canal repair</td>
<td>3</td>
</tr>
<tr>
<td>Aortic arch repair</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
</tr>
</tbody>
</table>

autonomic responses due to a different volume status, hematocrit level, pump flow, temperature and inotropic or vasoactive drugs. On the other hand, relative anesthesia overdose may result in hypoperfusion and dysfunction of organs. For adults, observational studies have demonstrated an association between deep anesthesia, as measured by processed EEG monitoring and postoperative outcome. Nitzschke et al. demonstrated that BIS-guided titration of sevoflurane reduced the sevoflurane plasma concentration and decreased noradrenaline administration as compared to routine care during on-pump cardiac surgery. In 80 infants undergoing cardiac surgery, Jiang et al. demonstrated a decrease in the consumption of anesthetics, more stable hemodynamics and quicker recovery and extubation when total intravenous anesthesia was guided by Narcotrend monitoring.

An advantage of the Narcotrend over other processed EEG monitors in measuring the depth of anesthesia in children is that it takes the patient's age into account. It checks the EEG signal during anesthesia with regard to the level of EEG differentiation. If an EEG recorded during anesthesia has a low level of differentiation, the Narcotrend monitor only displays EEG classification for EEG segments with implied or clear suppression periods and EEG segments without suppression periods are indicated as undifferentiated EEG. The ability of the Narcotrend monitor to display “undifferentiated EEG”, “artefact” or “EMG” reduces the risk of indicating a wrongly calculated NI.

In our study, we observed a strong correlation between Narcotrend Index and nasopharyngeal temperature, even if the sevoflurane administration during hypothermia was gradually reduced. According to the Narcotrend indicating very deep anesthesia or burst suppression, administration of sevoflurane could have been reduced more during hypothermia. This was probably not done due to the fact that Narcotrend monitoring during pediatric cardiac surgery was, at our institution, introduced not long before the start of this observational study and, in the beginning, attending anesthetists and perfusionists were not familiar with the phenomenon of reduced anesthetic requirements during hypothermia. During the further course of this study, the mean dose of sevoflurane during hypothermia was reduced more and more. At present, at our clinic, we reduce the administration of sevoflurane during hypothermia and increase it during rewarming in accordance with the results of processed EEG monitoring. Further studies are needed to examine the influence of this approach on demand for vasopressor therapy and outcome.

For adults, decreased body temperature has been correlated with a decrease in MAC of inhalational anesthetics by other authors. Hypothermia reduces brain cellular electrical activity and overall body metabolism. It increases the threshold of reaction to external stimuli and has additive influence on the depth of anesthesia. When body temperature falls to 32°C, the EEG starts to be suppressed, burst-suppression patterns appear at approximately 24°C and electrocerebral silence at approximately 18°C, with a high degree of interpatient variability.

In addition to the hypnotic effect of hypothermia, several other mechanisms may be responsible for the decrease of anesthetic requirements during hypothermia. The solubility of sevoflurane in the lipid membrane increases with lower temperatures, resulting in possibly more potent effects on the cellular level. Physiological functions such as protein binding, binding to receptors, liver and kidney function and metabolic rate may also be altered. The decreased cerebral metabolic rate and oxygen consumption during hypothermia results in higher cerebral venous oxygenation; this can be
visualized by NIRS and was also observed in this study. The inverse correlation between NI and NIRS was most probably caused by the fact that hypothermia decreased NI and increased NIRS. Stein et al. found a weak, but statistically significant association between BIS and mixed venous oxygen saturation in 41 adults during hypothermia, but no association at body temperatures above 34.1°C. There are many factors (e.g., hematocrit, perfusion) other than metabolic rate alone which affect NIRS and mixed venous oxygenation. We did not observe events of critical NIRS drop, therefore, we cannot conclude in what way this would influence NI.

Special attention should be paid to the rewarming phase of CPB, because changes in the cerebral metabolic rate and in the gas characteristics may lead to increased anesthetic requirements. In adults, this could be demonstrated for sevoflurane and isoflurane. Laussen et al. reported an increase in BIS during the rewarming phase after mild hypothermic CPB in children under isoflurane anesthesia. They concluded that this increase could reflect an increase in consciousness level and is consistent with the reported risk for awareness during this phase of cardiac surgery. Therefore, after reducing the administration of volatile anesthetics during hypothermia, administration should be increased during the rewarming phase according to the results of processed EEG monitoring.

Due to the fact that the study design was observational, there are some limitations. We did not influence decisions about anesthetic or perfusion management and the child’s scheduled operation continued as per usual practice during data collection. Therefore, we were unable to randomize the patients into groups of different fixed sevoflurane concentrations or body temperatures. However, the range was broad enough for a significant statistical analysis. It is not sure whether the expiratory gas sampled from the sole expiratory port of the oxygenator reflects the real blood sevoflurane concentration. As mentioned above, pharmacokinetic and pharmacodynamic properties of anesthetic drugs during CPB are very difficult to predict. While we could exclude inadequately low cerebral oxygenation by using NIRS, other aspects of cerebral perfusion during CPB could have introduced confounding factors into this study. And, like all EEG monitors, the Narcotrend is based on primarily normothermic conditions, but the algorithm calculated depth of anesthesia according to the slowing of the EEG patterns and this can also be observed during loss of consciousness due to hypothermia. In a study of patients on CPB, Dewandre et al. did not observe any effect of surgical stimulation on BIS during hypothermia and stable anesthesia. They concluded that EEG was reliable in assessing the hypnotic affects during normothermic or mild hypothermic CPB.

In conclusion, perfusionists and anesthetists should be aware of the results of processed EEG monitoring during CPB. Sevoflurane requirements differ inter-individually, may decrease during cooling and increase during rewarming. Therefore, it seems reasonable to include the results of processed EEG monitoring when administering sevoflurane during CPB in children, but further studies are necessary to confirm this thesis.

Declaration of Conflicting Interests
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References
4. Monk TG, Weldon BC. Anesthetic depth is a predictor of mortality: it’s time to take the next step. Anesthesiology 2010; 112: 1070–1072.
8. Antognini JF. Hypothermia eliminates isoflurane requirements at 20 degrees C. Anesthesiology 1993; 78: 1152–1156.