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Cerebral and Systemic Hemodynamic Effects of Intravenous Bolus Administration of Propofol in Neonates

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Key Words
Propofol · Preterm neonates · Cerebral tissue oxygenation index · Fractional tissue oxygen extraction · Near-infrared spectroscopy

Abstract
Objectives: To assess variability of systemic hemodynamics and its covariates following bolus propofol administration in (pre)term neonates, and to analyze the effect of propofol on cerebral tissue oxygenation index (TOI) and fractional tissue oxygen extraction measured by near-infrared spectroscopy. ***Methods:*** In (pre)term neonates, we recorded mean arterial blood pressure (MABP), saturation (SaO_2), heart rate (HR) and TOI from 5 min before up to 60 min after intravenous bolus propofol (3 mg kg^{-1}) administration during elective chest tube removal. Covariate analysis included postmenstrual age (PMA ≤ or >37 weeks), postnatal age (PNA ≤ or >10 days), comedication (fentanyl +/– midazolam) and congenital cardiopathy (yes/no). Fractional tissue oxygen extraction was calculated as (SaO_2 – TOI)/SaO_2. ***Results:*** Twenty recordings in 19 neonates were assessed. Following propofol administration, an abrupt, minor decrease in HR and SaO_2 was seen with fast recovery, while MABP decreased up to 1 h. TOI decreased during the first 3 min, reflecting an imbalance between cerebral oxygen delivery and demand. Despite sustained decrease in MABP, TOI then returned to baseline, suggesting a better balance between oxygen delivery and demand. PNA ≤10 days, comedication and absence of cardiopathy were associated with more subtle decreases in cerebral oxygenation and faster recovery. ***Conclusions:*** Propofol-induced decrease in HR, SaO_2 and cerebral oxygenation is short lasting while a decrease in MABP is observed up to 60 min. The variability in the effects of propofol is influenced by PNA, comedication or cardiopathy. Near-infrared spectroscopy can be used to assess hemodynamic effects of hypnotics on the cerebral oxygenation.

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Introduction

Propofol (2,6 di-isopropylphenol) is a short-acting anesthetic that is rapid in onset and short in duration. Because of these characteristics, propofol became a frequently administered drug for induction of anesthesia or for (procedural) sedation in adults or children and more recently, in neonates. Elimination kinetics are triphasic and characterized by fast metabolic clearance. Due to ontogeny, propofol clearance in neonates is lower compared to children and displays extensive interindividual variability [1]. Covariates of the interindividual variability of propofol clearance in neonates are postnatal (PNA) and postmenstrual age (PMA) [2]. Data on propofol phar-

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macodynamics in newborns are limited and conflicting [3–5].

Ghanta et al. [4] recently reported on the pharmacodynamics of intravenous bolus propofol (2.5 mg kg^{-1}) in 33 preterm neonates during semielective endotracheal intubation. Compared to a morphine/atropine/suxamethonium regimen, time until sleep or muscle relaxation and time to achieve successful intubation were shorter. Median time of recovery, defined by regain of the first spontaneous voluntary movements was 780 s (range 360–1,110). During intubation, there was a drop in saturation and heart rate (HR) without decrease in blood pressure. Changes in vital signs were less pronounced in neonates to whom propofol was administered. This blunted impact on blood pressure and the fast recovery of oxygenation is somewhat in contrast with another observation in 21 neonates to whom intravenous bolus propofol (2 mg kg^{-1}, combined with fentanyl 1.5 μg kg^{-1}) was administered for endotracheal intubation for respiratory distress. In 7/21 (33%) cases, a brisk oxygen desaturation developed despite adequate chest excursion. In most of these neonates, desaturation was associated with a transient decrease in systemic blood pressure [3]. Similar observations in 3 term neonates were reported by Veyckemans [5].

These conflicting results indicate the need to further explore the effect of propofol pharmacodynamics in neonates. We therefore prospectively evaluated the interindividual variability of systemic hemodynamics and the potential covariates during and following intravenous bolus propofol (3 mg kg^{-1}) administration during elective chest tube removal in a heterogeneous cohort of (pre)term neonates. Since near-infrared spectroscopy (NIRS) can be used to study the effects of drug administration on the cerebral neonatal oxygenation [6], we used this tool to further document the effects of propofol on the neonatal cerebral tissue oxygenation index (TOI) and fractional tissue oxygen extraction (FTOE).

Patients and Methods

Clinical Characteristics, Ethics and Procedural Sedation Model

Neonates were included following approval of the study protocol by the ethical board of the University Hospital, Leuven, Belgium, and after informed written consent was obtained from the parents. The decision to prescribe propofol (3 mg kg^{-1} intravenous bolus over 10 s, Diprivan® 1%; Braun, Diegem, Belgium) for scheduled short procedural sedation was made by the attending neonatologist. Neonates had to be cardiovascular and respiratory stable, as judged by the attending neonatologist and on respiratory support. The aim of propofol (co)administration was to attain a short-lasting sedation to facilitate chest tube removal and avoid external aspiration of air [7].

Table 1. Mean (range) clinical characteristics of the study population at assessment

Weight at inclusion, g	2,931 (855–4,380)
Low birthweight (<1,500 g)	2 (855–1,300)
GA, weeks	35 3/7 (26–40)
PMA, weeks	37 6/7 (27–47)
PNA, days	18 (3–71)
Preterm/term (≤37/>37 weeks PMA)	6/14
Extremely preterm (<28 weeks PMA)	1
Young/older (≤10/>10 days PNA)	9/11
Male/female	16/4
Length, cm	47.8 (34.5–53)
Head circumference, cm	33.4 (24.5–37)
Apgar 1	7 (4–9)
Apgar 5	8 (4–10)
Cardiopathy (yes/no)	10/10
Comedication (fentanyl/fentanyl + midazolam/no)	6/8/6

Clinical characteristics were registered at inclusion [postmenstrual age (PMA, weeks), gestational age (GA, weeks), PNA (days), weight, creatinemia, clinical indication for initial chest tube placement and associated cardiopathy (defined as any structural cardiac anomaly, including symptomatic PDA)]. Propofol was administered in addition to the analgesics already administered by either continuous (fentanyl or tramadol) or intermittent (paracetamol) intravenous infusion. Chest tube removal was initiated as soon as sedation and relaxation were achieved as judged by the care-taking physician, routinely 30–60 s after administration of propofol. This procedural sedation model has already been used to describe the pharmacodynamics of methohexital during chest tube removal in neonates [7]. Neither dose nor type of analgesic was standardized since these analgesics were titrated based on systematic evaluation of pain during neonatal stay [8].

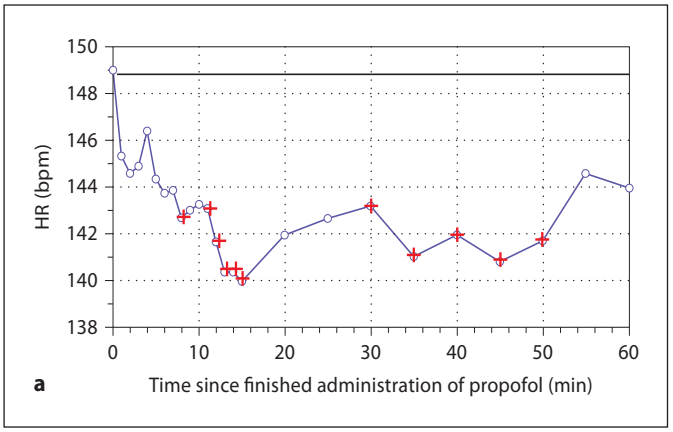
Pharmacodynamics

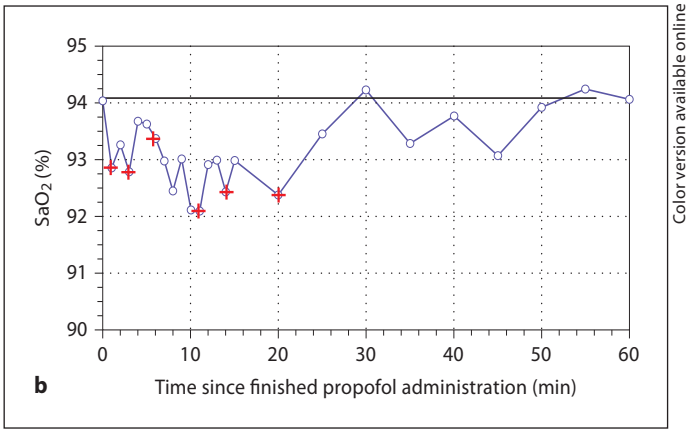
Vital Signs

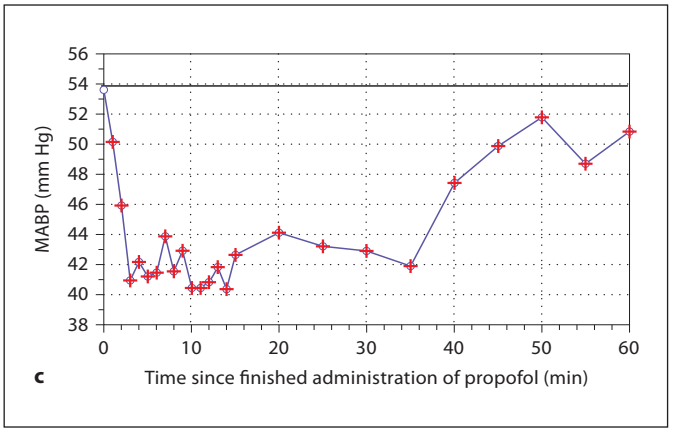
HR, mean arterial blood pressure (MABP) and arterial oxygen saturation (SaO_2; Pulse Oximeter, Novametrix®, USA) were recorded continuously and simultaneously with a sampling frequency of 100 Hz by the Codas system (Dataq Instruments®, USA), from 5 min before up to 60 min after the administration of propofol.

Cerebral Hemodynamics

Cerebral hemodynamics were measured with the NIRO 300 (NIRO 300; Hamamatsu®, Hamamatsu City, Japan). This device uses NIRS to measure changes in oxygenated hemoglobin (ΔHbO_2), reduced hemoglobin (ΔHbR) and total hemoglobin (ΔHbT) of the brain. With spatially resolved spectroscopy an absolute value, which reflects cerebral oxygenation, can be measured, i.e. the TOI [TOI (%) = $kHbO_2/(kHbO_2 + kHbR)$]. The NIRO 300 optodes were placed at the right frontoparietal side of the infant with a 4-cm interoptode distance and a differential path length factor of 4.39. The data were recorded in an analog







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Fig. 1. Median relative changes in HR (**a**), SaO_2 (**b**) and MABP (**c**) after propofol administration. The horizontal line represents the baseline value. Significant changes ($p < 0.05$) from baseline are marked (+).

way with a sampling frequency of 6 Hz by the data acquisition system Codas (Dataq Instruments). To investigate the balance between oxygen delivery (OD) and consumption, we calculated the FTOE, which reflects the fractional oxygen extraction as $(SaO_2 - TOI)/SaO_2$ [9].

Covariate Analysis and Statistics

From the individual recorded data, median values and interquartile range (IQR) over 1-min periods (up to 15 min after administration) and over 5-min periods (from 15 to 60 min after administration) were calculated. Baseline values of vital signs and cerebral parameters were determined as the median of the 3rd and 4th min before propofol administration. Relative to baseline values, changes in parameters up to 60 min after propofol administration were calculated as %Δ parameter = [(measured parameter – baseline parameter)/baseline parameter] × 100. From these individual data sets, median values over the whole group were calculated.

For statistical analysis, Medcalc® v9.2.0.2 and STATISTICA® for Windows (StatSoft, Inc., Tulsa, Okla., USA) were used. Over the whole group as well as for each patient individually, we used the paired Wilcoxon test to analyze trends and procentual changes (%Δ) in parameters.

The Mann-Whitney U test was used to verify whether the effect of propofol on cerebral oxygenation was influenced by covariates such as PMA (dichotomous, < or ≥37 weeks), PNA (< or ≥10 days), co-medication (fentanyl/+midazolam) or congenital cardiopathy (yes/no). A p value <0.05 was considered statistically significant.

Results

Data on cerebral and systemic hemodynamics were prospectively collected during 20 recordings in 19 preterm and term neonates (in 1 case, propofol was administered at two occasions on different days). Clinical characteristics are provided in table 1.

Systemic and Cerebral Hemodynamics after Propofol Administration (Group)

Median HR at baseline was 149.2 bpm (IQR = 22.7). Significant decreases from baseline were seen at 8 min, between 11 and 15 min and between 30 and 50 min after propofol administration. The most pronounced decrease was seen at 15 min (median %ΔHR = –6.1%; fig. 1a).

Median SaO_2 at baseline was 94.0% (IQR = 3.9). At 1, 3, 6, 11, 14 and 20 min after propofol administration, SaO_2 was significantly lower than baseline with subsequent return to baseline. The most pronounced decrease was seen at 11 min (median $\%\Delta SaO_2$ = –2.0%; fig. 1b).

MABP was only recorded in neonates with an arterial line (13/20). Median baseline MABP was 53.6 mm Hg (IQR = 7.5). MABP remained significantly lower than baseline up to 60 min after propofol administration. The most pronounced decrease in MABP was seen at 14 min (median %ΔMABP = –24.5%) with a subsequent return to baseline (fig. 1c).

Median TOI at baseline was 63.9% (IQR = 9.2). TOI was significantly lower than baseline up to 3 min after administration of propofol. At the 1st min %ΔTOI = –4.4% (p = 0.002). At the 2nd min, the decrease in TOI was most pronounced (%ΔTOI = –5.0%; p = 0.016) with subsequent return to baseline at the 3rd min (%ΔTOI = –2.5%; p = 0.033; fig. 2). Median FTOE at baseline was 0.31% (IQR = 0.088) and was not significantly different from baseline after the administration of propofol.

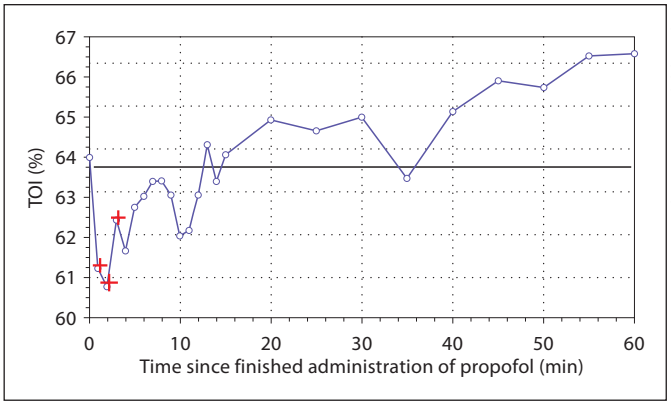


Fig. 2. Median relative changes in TOI after propofol administration. The horizontal line represents the baseline value. Significant changes ($p < 0.05$) from baseline are marked (+).

Covariates of Interindividual Variability

PMA ≤37 Weeks versus PMA >37 Weeks

With propofol administration, the relative changes in HR, MABP, SaO_2, TOI and FTOE were not significantly different between term (PMA >37 weeks) and preterm (PMA ≤37 weeks) infants.

PNA ≤10 Days versus PNA >10 Days

With propofol administration, relative changes in HR, SaO_2 and MABP were not significantly different between the neonates with PNA ≤10 days or PNA >10 days. However, at 8 (p = 0.0034), 10 (p = 0.012), 11 (p = 0.026) and 12 (p = 0.033) min after propofol administration, TOI was 2% higher than baseline in neonates with PNA ≤10 days versus 8% lower in neonates with PNA >10 days (fig. 3a). At 5 (p = 0.033), 6 (p = 0.047) and 7 (p = 0.039) min, FTOE was 0.76% lower than baseline in neonates with PNA ≤10 days versus 7.3% higher than baseline in infants with PNA >10 days (fig. 3b).

Comedication (Yes/No)

With administration of propofol HR, SaO_2 and MABP were not significantly different between neonates either or not cotreated with fentanyl (and midazolam). However, at 13 (p = 0.015), 14 (p = 0.041), 15 (p = 0.019), 30 (p = 0.009) and 35 (p = 0.014) min TOI was approximately 3.7% higher than baseline in infants receiving both fentanyl and midazolam versus 5.4% lower than baseline in infants receiving no comedication at all (fig. 3c). At 8 (p = 0.043), 9 (p = 0.027), 11 (p = 0.033), 12 (p = 0.006), 13 (p = 0.003), 14 (p = 0.012), 15 (p = 0.010) and 30 (p = 0.03) min, FTOE was 8.7% higher than baseline in infants receiving no comedication versus 4.72% lower than baseline in infants receiving both midazolam and fentanyl (fig. 3d).

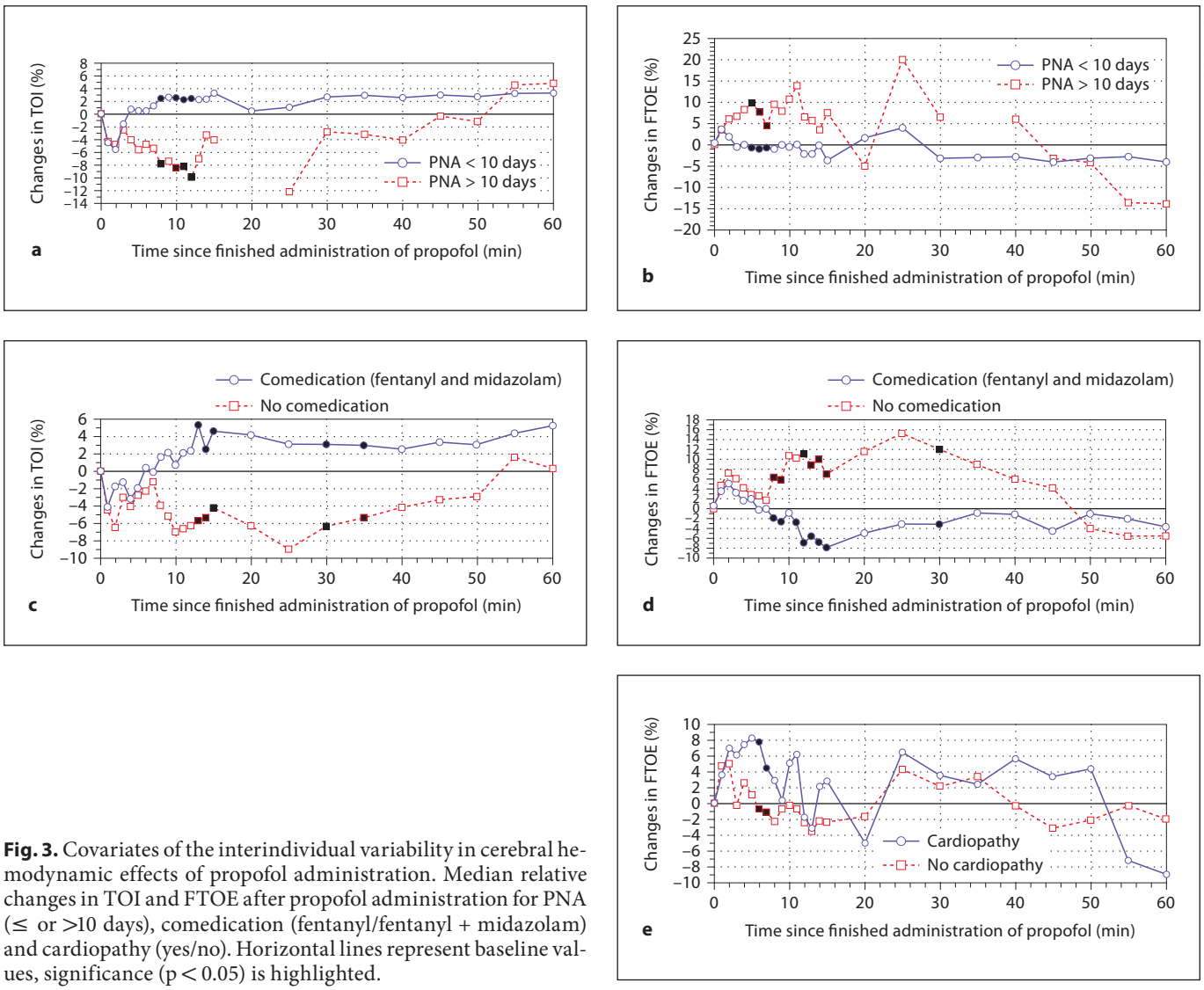
Cardiopathy versus No Cardiopathy

With propofol administration, relative changes in HR, SaO_2, MABP, and TOI were not significantly different between neonates with or without cardiopathy. However, at 6 (p = 0.010) and 7 (p = 0.03) min, FTOE was 0.66% lower than baseline in infants without cardiopathy versus 6.1% higher than baseline in infants with cardiopathy (fig. 3e).

Discussion

Data on the pharmacodynamic effects of propofol in neonates are limited and conflicting, and interindividual variability is suggested. Its use in endotracheal intubation has been reported [3–5]. In contrast with this model, the current chest tube removal model enabled us to evaluate the effects of intravenous bolus propofol administration on the cerebral and systemic hemodynamics in neonates and to assess the influence of covariates in the explanation of interindividual variability.

Compared to baseline vital signs, we hereby documented a modest and short-lasting decrease in HR (of max. 6%) and in peripheral oxygen saturation (of max.



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Fig. 3. Covariates of the interindividual variability in cerebral hemodynamic effects of propofol administration. Median relative changes in TOI and FTOE after propofol administration for PNA (≤ or >10 days), comedication (fentanyl/fentanyl + midazolam) and cardiopathy (yes/no). Horizontal lines represent baseline values, significance ($p < 0.05$) is highlighted.

2%). In contrast, a relevant and long-lasting (up to 60 min) impact on MABP (of max. 24.5%) was documented. This condition of relative stable HR and SaO_2 with propofol administration confirms other studies [4, 10–13]. However, also a brisk oxygen desaturation and profound hypoxemia have been reported in neonates [3].

In contrast, we found a more pronounced, longer-lasting decrease in MABP with administration of propofol; most prominent (–25%) at 14 min with a subsequent trend to return to baseline, although still significantly different from preadministration values at 60 min. This propofol-induced decrease in MABP is most likely the result of vasodilatation. Transient hypotension with propofol administration has been reported in many studies in adults and children [3, 14–17]. In neonates, however, only three studies report about the effect of propofol on MABP: Ghanta et al. [4] found a slight, nonsignificant increase in MABP during propofol (2.5 mg kg^{-1}) sedation for semielective intubation. Papoff et al. [3] reported a brisk oxygen desaturation with a transient decrease in systemic blood pressure when propofol (2 mg kg^{-1}) and fentanyl (1.5 μg kg^{-1}) were administered, and Veyckemans [5] reported profound hypoxemia and systemic hypotension after administration of 3 mg kg^{-1} propofol. As soon as hypotension was cured, oxygenation improved. The discrepancies with our study can be explained by differences in procedure (chest tube removal versus endotracheal intubation), in measurement technique (invasive versus

noninvasive blood pressure measurement) or in dosing (3 versus 2 and 2.5 mg kg^{-1}). Despite a pronounced decrease in MABP, we did not find tachycardia probably due to the inhibitory effect of propofol on the baroreceptor reflex [10–13].

Changes in MABP can cause changes in cerebral blood flow (CBF) if autoregulation is impaired, which is often seen in premature infants during the first days of life [18]. Propofol-induced hypotension might therefore reduce CBF and cerebral oxygenation [19, 20]. However, the effect of propofol on the brain can also be caused by a direct effect since propofol acts as a global central nervous system depressant by suppression of the cerebral electrical and metabolic activity: it directly activates $GABA_A$ (γ-aminobutyric acid) receptors and inhibits the N-methyl D-aspartate receptor [21–24], whereas the cerebral metabolic rate of oxygen ($CMRO_2$) decreases [19–21, 25–28]. With intact neurovascular coupling, we expected no change in cerebral oxygenation because of a decrease in CBF. At the first 3 min after propofol administration, however, we saw an acute, short-lasting decrease in TOI and a slight increase in FTOE, suggesting that the systemic decrease in MABP and its associated decrease in CBF outweigh the anticipated decrease in cerebral oxygen consumption due to sedation. After 3 min, FTOE and TOI returned to baseline, suggesting a better coupling between OD and consumption, despite the sustained decrease in MABP which seemed to have no further influence at that moment. In concordance with our findings, Hung et al. [14] found a lower regional cerebral oxygen saturation (rSO_2) after propofol induction in young and elderly patients and suggest that this was induced by hypotension. Despite a decrease in MABP of 30% up to 5 min after administration, they saw a quick return to baseline of rSO_2, suggesting an increase in fractional oxygen extraction with propofol administration.

Besides general trends, we also tried to unveil covariates of the interindividual variability in systemic and cerebral hemodynamic effects of this drug. In the current cohort PNA, comedication with midazolam +/– fentanyl and cardiopathy were defined as covariates explaining the interindividual variability in hemodynamic effects of propofol on the cerebral oxygenation. A decrease in cerebral oxygenation was seen immediately after propofol administration in all cases. Thereafter, however, and compared to preadministration values, the reaction of the brain to the continuation of sedation differs according to the covariates: in younger neonates (PNA ≤10 days) and in neonates cotreated with either midazolam and fentanyl, cerebral oxygenation returned faster to preadministration baseline levels.

Reduced propofol clearance in infants with PNA ≤10 days has been reported [2]. We therefore anticipated seeing a shorter and more transient effect of propofol on cerebral hemodynamics in older neonates. In contrast, slower return to baseline values was seen. This can be explained by relative higher propofol clearance with concomitant enhanced increase in cerebral activity and subsequent oxygen demand while oxygen supply is still low because of the sustained decrease in MABP and CBF. In a pharmacokinetic study, PMA and PNA were defined as covariates in the interindividual variability in propofol pharmacokinetics [2]. In the current study, however, PMA was not found to be a covariate in the hemodynamic effects of propofol on the cerebral oxygenation. This might be explained by the heterogeneous study population (6 preterm versus 14 term infants). It also suggests that covariates of pharmacodynamics differ from covariates of pharmacokinetics.

Besides PNA, the current observations suggest that the additional effect of propofol on the cerebral oxygenation is influenced by comedication: in contrast to the slow recovery of TOI in infants who were not comedicated, fast return to baseline values was seen in infants to whom fentanyl +/– midazolam together with propofol was administered. This can be explained by comedication-induced systemic decrease in MABP or by metabolic depression. Firstly, hypotension with fentanyl +/– midazolam comedication, whether or not caused by midazolam [29], has been reported in neonates [30, 31]. We lack sufficient MABP recordings to prove comedication-induced hypotension, but we suggest that additional administration of propofol has no extra effect on the reduced MABP, and subsequent the CBF and OD, which allows TOI to recover rapidly. Secondly, it might be that the comedication-induced high degree of cerebral metabolic depression outweighs the decrease in CBF and oxygen supply that is induced with sedation. Unfortunately, we did not record clinical sedation scores or recovery characteristics during propofol sedation to prove this. Finally, cardiopathy had only a limited, but significant, influence on the propofol-induced effect on FTOE. The most pronounced and long-lasting depressions in cerebral oxygenation were observed in 4 full-term, cardiac patients without comedication and with a PNA >10 days. However, based upon these study results we are not able to differentiate to which extent the covariates influence the cerebral oxygenation or whether colinearity exists.

In conclusion, the propofol-induced decrease in HR, SaO_2 and cerebral oxygenation is short-lasting, while a decrease in MABP is observed for up to 60 min. The variability in the effects of propofol is influenced by PNA, comedication or cardiopathy. Until more experience with this drug in neonates is reported, we recommend using this drug cautiously. NIRS can be used to assess the (hemodynamic side) effects of hypnotic drugs on cerebral oxygenation.

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