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RESEARCH REPORT

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Modeling iatrogenic intraoperative hyperthermia from external warming in children: A pooled analysis from two prospective observational studies

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Abstract

Background: Maintenance of normothermia is an important quality metric in pediatric anesthesia. While inadvertent hypothermia is effectively prevented by forced-air warming, this therapeutic approach can lead to iatrogenic hyperthermia in young children.

Aims: To estimate the influence of external warming by forced air on the development of intraoperative hyperthermia in anesthetized children aged 6 years or younger.

Methods: We pooled data from two previous clinical studies. Primary outcome was the course of core temperature over time analyzed by a quadratic regression model. Secondary outcomes were the incidence of hyperthermia (body core temperature >38°C), the probability of hyperthermia over the duration of warming in relation to age and surface-area-to-weight ratio, respectively, analyzed by multiple logistic regression models. The influence of baseline temperature on hyperthermia was estimated using a Cox proportional hazards model.

Results: Two hundred children (55 female) with a median age of 2.1 [1st–3rd quartile 1–4.2] years were analyzed. Mean temperature increased by 0.43°C after 1 h, 0.64°C after 2 h, and reached a peak of 0.66°C at 147 min. Overall, 33 children were hyperthermic at at least one measurement point. The odds ratios of hyperthermia were 1.14 (95%-CI: 1.07–1.22) or 1.13 (95%-CI: 1.06–1.21) for every 10 min of warming therapy in a model with age or surface-area-to weight ratio (ceteris paribus), respectively. Odds ratio was 1.33 (95%-CI: 1.07–1.71) for a decrease of 1 year in age and 1.63 (95%-CI: 0.93–2.83) for an increase of 0.01 in the surface-to-weight-area ratio (ceteris paribus). An increase of 0.1°C in baseline temperature increased the hazard of becoming hyperthermic by a factor of 1.33 (95%-CI: 1.23–1.43).

Conclusions: In children, external warming by forced-air needs to be closely monitored and adjusted in a timely manner to avoid iatrogenic hyperthermia especially

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during long procedures, in young age, higher surface-area-to-weight ratio, and higher baseline temperature.

KEYWORDS
anesthesia, body temperature, child, hyperthermia, warming strategy

1 | INTRODUCTION

Perioperative temperature management is one of the key elements for pediatric anesthesiologists.[1,2] It requires an accurate measurement of the patient's core temperature and an appropriate warming strategy aimed at maintaining normothermia. Since infants and small children are at high risk for temperature perturbations,[3] majority of research has been focusing on the prevention of inadvertent intraoperative hypothermia (defined as body core temperature below 36.0°C),[4,5] which to date can be successfully achieved by the aid of forced-air warming devices.[6,7] However, as a result of aggressive forced-air warming, a new emerging issue is iatrogenic intraoperative hyperthermia in children.[8]

Intraoperative hyperthermia is defined as body core temperature above 38.0°C.[5] It can lead to increased basal metabolic rate and sympathetic activity,[9] higher oxygen demand and is associated with an increased risk of surgical site infections in infants.[10] While a large multi-center study in adults has recently shown that keeping core temperature at least 35.5°C rather than aggressively warming to 37°C throughout the perioperative period may be sufficient to prevent temperature-related complications,[11] little is known about the minimal ideal core body temperature that would prevent perioperative adverse outcomes in pediatric anesthesia. For this reason, the pediatric care warming strategy is still aggressive and aims at preventing hypothermia rather than hyperthermia, resulting in unintended iatrogenic hyperthermia in up to 26.5% of cases among children between 1 and 2 years of age.[8] This finding is supported by two recent prospective observational studies conducted by our study group,[12,13] leading us to investigate whether and how the warming strategy currently used could contribute to a steady increase in core temperature over time.

We hypothesized that our warming strategy, mainly depending on forced-air, carries the risk of excessive warming and development of hyperthermia. We tested this hypothesis by pooling the primary data from our two recent prospective observational studies and analyzing the course of core temperature of anesthetized children aged 6 years or younger, to estimate the influence of external warming on the development of intraoperative hyperthermia. Further, we fitted models to derive probabilities for the risk of hyperthermia, aiming to identify potential risk factors and possible strategies for the prevention of intraoperative hyperthermia.

What is already known

Forced-air warming effectively prevents pediatric perioperative hypothermia.

What this article adds

Children with long procedures, young age, high surface-area-to-weight ratio, and high baseline temperature are at risk for iatrogenic hyperthermia with the use of forced-air warming. Clinicians should pay attention to adjust warming settings on time.

2 | METHODS

We pooled individual patient data from two prospective, single-center observational studies, assessing the agreements of noninvasive temperature monitoring devices against standard esophageal core temperature in children.[12,13] The studies were approved by the Institutional Review Board of the University Medical Center Goettingen, Goettingen, Germany (25/1/19 and 22/2/21, respectively) and registered in the German Clinical Trials Register (DRKS00016655 and DRKS00024703, respectively). Periods of recruitment were from April to September 2019 and from April to July 2021. Written informed consent from parents or legal guardians as well as children assent were obtained before enrollment. We adhered to the STROBE guidelines for reporting of observational studies.[14]

2.1 | Subject selection

Both aforementioned studies each included 100 children aged 6 years or younger who underwent surgery with a scheduled operation time greater than 30 min requiring general anesthesia. Exclusion criteria were refusal to participate from the parents, legal guardians, or the child; contraindications for the insertion of an esophageal temperature probe, that is, esophageal atresia or hypertrophic pyloric stenosis; and procedures in which the location of the esophageal temperature probe would interfere with the surgical field.

2.2 | Protocol

Our studies followed the applied warming strategy as shown in Figure 1. Children were kept dressed in the holding area and the operating room was prewarmed to a temperature of 24.5°C. Upon arrival in the operating room, anesthesiology personnel allowed children to lay on a prewarmed pediatric underbody blanket (Moeck Warming System™, Hamburg, Germany) placed on the operating room table

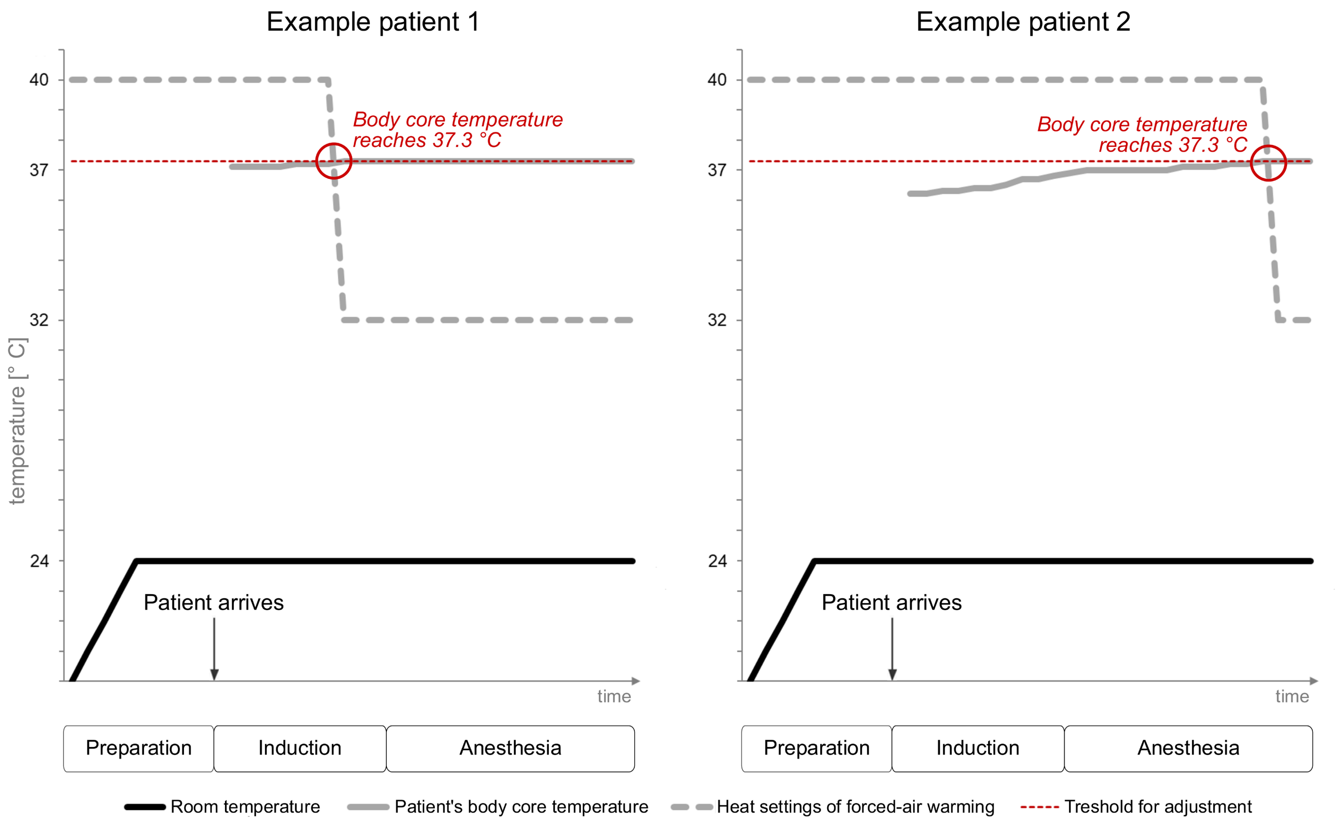

FIGURE 1 Schematic illustration of the applied warming strategy with regards to room temperature (black line), heat settings of forced-air warming system (gray dashed line) and patient body core temperature (gray) in two example patients. Whether body core temperature reaches the threshold of 37.3°C (red dashed line, encircled) early (left panel, example patient 1, during induction of anesthesia) or late (right panel, example patient 2, during general anesthesia), we adjusted the heat settings of the forced-air warming system according to our standards.

before cloth removal and establishment of standard monitoring. The forced-air warming was continuously running during undressing, induction of anesthesia, prepping, draping, and surgery. After induction of general anesthesia, noninvasive temperature monitoring devices were applied to each patient. An esophageal temperature probe (RÜSCH Pharyngeal Temperature Sensor™, Teleflex Medical, Athlone, Ireland) served as the reference method for core temperature in both studies. The esophageal probe was inserted according to the formula of Whitby and Dunkin aiming to place its tip in the distal fourth of the esophagus.[15] Baseline temperature was measured after securing the airway when the esophageal probe reached equilibration to reflect valid values for core temperature.

Balanced or total intravenous anesthesia was administered according to the discretion of the attending anesthesiologist. For active warming therapy, the forced-air warming system was set on the highest heat setting allowed in the manufacturer's manual for pediatric use (40°C) in each patient. As per our standards, forced-air warming temperature was reduced to 32°C by the attending anesthesiologist when core temperature reached 37.3°C. After anesthesia induction and surgical preparation, the child was covered with a coated surgical drape (Raucodrape® Pediatric Basic Set, Lohmann & Rauscher, Rengsdorf, Germany), consisting of a combination of polypropylene-flees and polyethene-foil. Anesthetic gases were passively warmed through heat and moisture exchange filters. In our cohort, no overhead heater was used. Infusion warming was not routinely used for fluid maintenance, however, in cases where additional large fluid boluses or transfusion of blood products were required a fluid warming device was used.

2.3 | Data processing and outcomes

While the first study recorded temperature values in five-minute intervals until the emergence of anesthesia,[12] the second study recorded temperature values in one-minute intervals.[13] The two datasets were harmonized by extracting common data elements items on baseline characteristics and treatment. Data collected included demographics (age, sex, height, weight), American Society of Anesthesiologists (ASA) physical status classification, indication for surgery, duration of warming, and surgical procedures for each patient. The surface-area-to-weight ratio was calculated using the surface estimation method by Haycock et al.[16] for children divided by weight. Hyperthermia was defined as core temperature above 38.0°C.[5]

Our primary outcome was to analyze the course of core temperature over time. Secondary outcomes were the incidence of hyperthermia and hypothermia, the probabilities of developing iatrogenic hyperthermia over the duration of warming in relation to age and surface-area-to-weight ratio, respectively, and the influence of baseline temperature on the incidence of iatrogenic hyperthermia.

2.4 | Statistical analysis

As this study used data from two clinical studies, no separate sample size calculation was performed.

Descriptive statistics were reported as numbers or median [1st–3rd quartile] as appropriate. If not stated otherwise, tests were performed two-sided on a significance level of 5%. Parameter estimates are provided with corresponding 95% confidence intervals (95%-CI). For the course of core temperature over time, we fitted a quadratic regression model and stated the corresponding regression parabola. The incidences were reported descriptively. For the probabilities of developing iatrogenic hyperthermia over the duration of warming, we fitted two multiple logistic regression models with explaining variables surface-area-to-weight ratio and duration of warming and age and duration of warming, respectively. Explanatory variables were selected using a backward stepwise model selection algorithm based on the Akaike information criterion including patients' characteristics as of Table 1 below. To assess the goodness of fit of the models, Chi^2-tests were performed. Furthermore, marginal distributions for both models were estimated. To assess the influence of baseline temperature, we fitted a Cox proportional hazards model with covariate baseline temperature. For further descriptive analyses of the variables age, height, weight, surface-area-to-weight ratio, and body mass index, we provided estimated univariate distributions (via histograms), scatterplots of all pairs, as well as their Pearson's correlation coefficient. Data were analyzed using R version 4.1.3 (The R Foundation for Statistical Computing, Vienna, Austria) with packages "survival" and "survminer" for the computation of event probabilities.[17,18]

3 | RESULTS

We analyzed 200 children from 5 days to 6.9 years of age with an actual duration of warming from 10 to 412 min. The participants' characteristics are presented in Table 1. Distributions and correlations between baseline patient characteristics are shown in Figure S1.

3.1 | Course of core temperature over time

The mean temperature increased by 0.43°C after 1 h (71 patients left), by 0.64°C after 2 h ($n = 25$) and reached a peak of +0.66°C at 147 min ($n = 13$) with respect to baseline temperature (Figure 2). The fitted mean temperature for a patient with duration of warming $t \in [0, 240]$ was $f(t) = a*t^2 + b*t + c$ with coefficients $a = -3.082$ (95%-CI: −3.781 to −2.372) $*10^{-5}$, $b = 9.052$ (95%-CI: 7.738 to 10.367) $*10^{-3}$, and $c = 37.026$ (95%-CI: 36.984 to 37.068).

3.2 | Incidence of hyperthermia and hypothermia

Overall, 33 children (16.5%) were hyperthermic at at least one measurement point, with no significant difference between males ($n = 22$, 11%) and females ($n = 11$, 5.5%) ($p = .543$). Three children were hyperthermic already at baseline because of infections. Twenty eight children were hyperthermic at the end of the measurements. In contrast, five children had temperatures below 36.0°C, of whom two were hypothermic already at baseline.

With regards to surgical procedures, hyperthermia occurred most frequently in hypospadias repairs (7 of 20, 35%), followed by inguinal herniotomy (2 of 15, 13.3%) and orchiopexy (6 of 48, 12.5%), respectively.

3.3 | Influence of age

With regards to age groups, hyperthermia occurred most frequently in infants (12 of 46, 26%) and 1-year-olds (12 of 51, 24%), with a peak in the age subgroup between 7 and 12 months (8 of 23, 35%, Table 2).

For every 10 min extension of warming (ceteris paribus), the odds ratio of hyperthermia was 1.14 (95%-CI: 1.07 to 1.22, Figure 3A). For every decrease in 1 year of age, the odds ratio of developing iatrogenic hyperthermia was 1.33 (95%-CI: 1.07 to 1.71, ceteris paribus).

3.4 | Influence of surface-area-to-weight ratio

For every 10 min extension of warming (ceteris paribus), the odds ratio of hyperthermia was 1.13 (95%-CI: 1.06 to 1.21, Figure 3B). For each increase of 0.01 in the surface-to-weight-area ratio, the odds ratio of hyperthermia was 1.63 (95%-CI: 0.93 to 2.83, ceteris paribus).

For both models of age and of surface-area-to-weight ratio, Chi^2-Goodness-of-Fit tests rejected the null model containing an intercept as the only variable in favor of the respective fitted model at the 5% level ($p < .001$). The marginal distributions for both models are shown in Figure S2.

3.5 | Influence of baseline temperature

The baseline temperature significantly affected the hazard of developing hyperthermia ($p < .001$). An increase of 0.1°C in baseline temperature increased the hazard of becoming hyperthermic by a factor of 1.33 (95%-CI: 1.23 to 1.43). The estimated probability of becoming hyperthermic at a time point t ϵ [0, 240] in dependence of the baseline temperature is shown by Figure 4.

4 | DISCUSSION

Our data showed a steady increase in body core temperature in children aged 6 years or younger who underwent surgery under general anesthesia and were warmed by forced-air. The increase in mean core temperature of more than 0.6°C within the first two and a half hours suggests that our management generally leads to excessive warming, resulting in hyperthermia in almost one out of six pediatric patients.

Perioperative temperature management aims at maintaining normothermia. While the ideal is a temperature-steady state course with almost no user intervention necessary,[7] our results demonstrate that additional research is needed since children under the age of two are particularly vulnerable to develop iatrogenic hyperthermia. The surface-area-to-weight ratio is the physical determinant responsible for this phenomenon and more appropriate than, for example, body mass index.[19] But the most common proxy for all determinations in daily routine is age, making age reporting more convenient for clinical providers. The risk of excessive warming is driven by the duration of warming, but more importantly, from the baseline temperature. Putting these findings together, it seems that achieving a core temperature steady state in young children without the need for user interventions appears difficult, especially in surgical procedures where multiple risk factors are combined. Our data show that iatrogenic hyperthermia most frequently occurred in hypospadias repair, most likely because this type of surgery is mainly performed in very young children, it usually lasts long, and the surgical field is small while the majority of the body is fully covered and insulated lowering significantly the likelihood of heat loss.[1] Similar procedures involving a limited surgical field and a significant insulation of the nonoperative body surface area, such as those performed in oral and maxillofacial surgery, have been associated with one of the highest incidence (27%) of iatrogenic hyperthermia in adults and children.[8]

TABLE 1 Patient characteristics

Patients	200 (55 female)
Age [years]	2.1 [1–4.2]
Height [cm]	89.9 [76–107]
Weight [kg]	12.6 [9.5–18]
Surface-area-to-weight ratio [m^2/kg]	0.0442 [0.0407–0.0482]
Duration of warming [min]	45 [30–80]
Type of surgery	
Urology[a]	97 (most: orchiopexy)
Visceral[a]	61 (most: herniotomy)
Trauma	18 (most: osteosynthesis)
Neurosurgery	16 (most: detethering)
Orthopedic	13 (most: repair of spine deformity)
Other	5

Note: Values are numbers or median [1st–3rd quartile].

[a]Ten patients had a combination of surgery at the same time, for example, urological and visceral surgery.

Forced-air warming has been associated with an increased risk of developing intraoperative iatrogenic hyperthermia in recent years.[6,8] Our findings are consistent with those of the retrospective analysis by Mittnacht et al.[8] in terms of the incidence (19.4% <6 years) and the age-specific odds of becoming hyperthermic. In addition, they also found the highest odds of developing iatrogenic hyperthermia in children aged 1 to 2 years,[8] although they set tighter inclusion criteria than we did, for example, by excluding all patients who had a baseline temperature higher than 37.0°C. On the contrary, they defined hyperthermia already as mean core temperature over 37.5°C. Witt et al.[6] reported an incidence of inadvertent hyperthermia (≥38°C) in eight out of 119 neonates and infants (6.7%) in their multicenter observational study evaluating the forced-air Moeck Warming System® that we currently use. In a similar study comparing two different forced-air warming systems, Triffterer et al.[7] reported inadvertent hyperthermia in seven out of 40 children (17.5%, mean age 13 months). They used a similar approach like we did by reducing the system's temperature setting when patient's temperature rose. However, while we set the core temperature target at 37.3°C before reducing the device temperature output, they set their target to 37.5°C.[7] Moreover, they measured rectal temperature, which is known to lag core temperature over time, particularly during rapid thermal perturbations.[20,21] This means that the incidence of hyperthermia could have been under-detected.

The reason why some children particularly under the age of 2 years develop hyperthermia is because very young children have a smaller thermal mass and a higher surface-area-to-weight ratio than adults.[22] While metabolic heat production is roughly proportional to body mass, cutaneous heat loss is roughly proportional to surface area.[1] This leads to an imbalance of heat loss and production in children explaining their greater susceptibility to environmental disturbances.[23] The consequence is that they become hypothermic much faster in a cold environment.[1] Therefore, on the one hand, children are prone to cool out very quickly, especially if clinical prewarming is not attained, contributing to the many side effects of hypothermia.[3] On the contrary, however, it enables external warming therapy to be so effective.[1,3]

Our applied warming strategy effectively prevents inadvertent hypothermia compared to reported incidences elsewhere.[3] However, it is still not as effective in preventing iatrogenic hyperthermia in high-risk patients and is therefore a possible metric to target for improving our current clinical practice. Three aspects become clear from our research: (1) effect of warming therapy should be monitored in pediatric anesthesia by measuring core temperature; (2) reduction in a timely manner of the output temperature

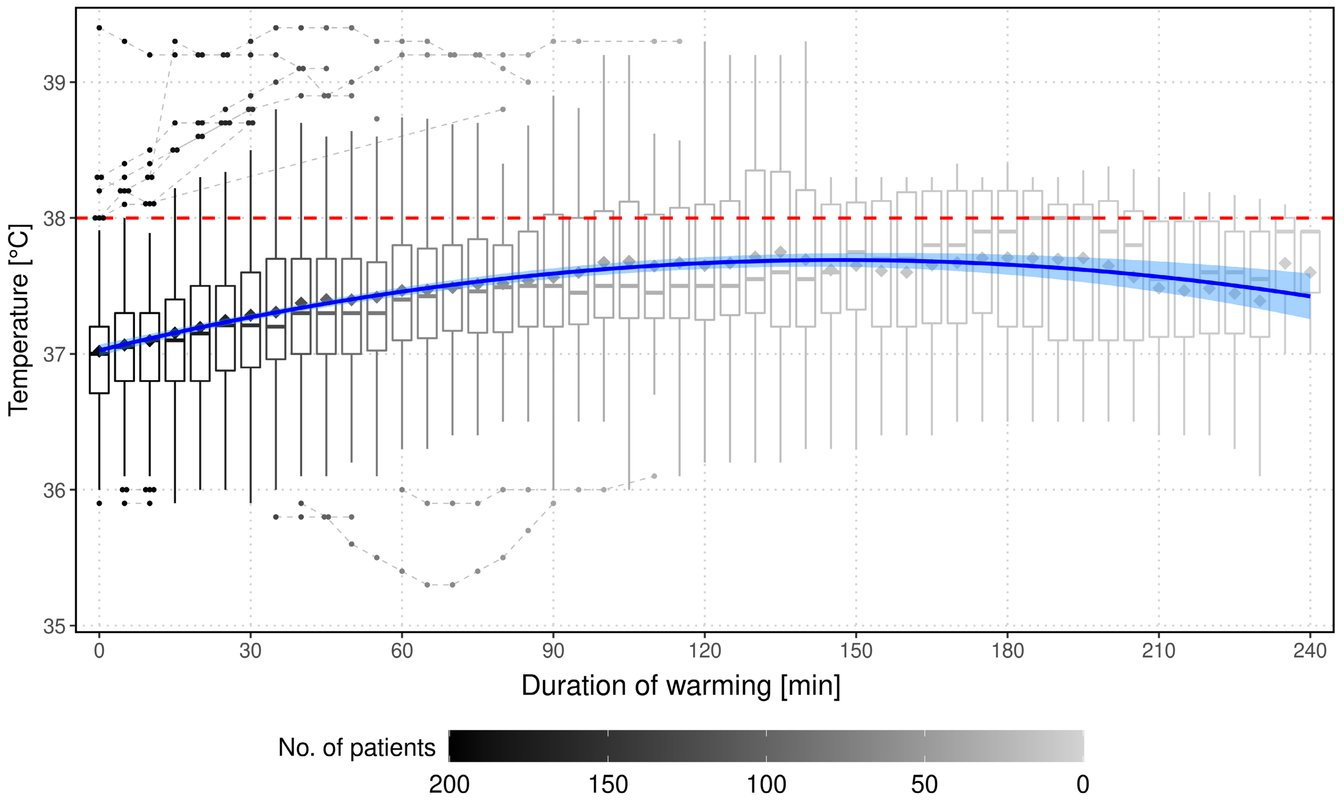

FIGURE 2 Course of temperature values in 5-min intervals over duration of warming by quadratic regression fit (dark blue) and corresponding 95% confidence band (light blue) based on 2623 measurements in 200 children with measurement time ≤240 min. The distribution of the temperature values for a given time are displayed as boxplots with additional means as diamond (◆). Color shading is according to the declining number of patients over time due to different duration of warming. Due to the large autocorrelation of measurements, extreme temperatures often appear for a longer period of time, which means that outliers close in time and temperature often correspond to the same patient (connected by lines).

TABLE 2 Distribution of age, height, weight, surface-area-to-weight ratio, and incidence of hyperthermia according to age

Age	*n* (% of total)	Height [cm]	Weight [kg]	surface-area-to-weight ratio [m^2/kg]	Hyperthermia (% of age group)
<1 month	3 (2%)	52.0 [49–52]	3.2 [2.9–3.3]	0.0679 [0.0669–0.0702]	0 (0%)
≥1 to ≤6 months	20 (10%)	61.5 [57.4–66.3]	6.0 [5–7.2]	0.0544 [0.0513–0.0573]	4 (20%)
≥7 to <12 months	23 (12%)	68.0 [68.5–78]	12.5 [8–10.3]	0.0481 [0.0465–0.0498]	8 (35%)
≥1 to <2 years	51 (26%)	79.0 [71.5–80]	11.0 [9.5–12]	0.0455 [0.0432–0.048]	12 (24%)
≥2 to <3 years	23 (12%)	92.0 [88–96]	13.0 [11.6–14.9]	0.0445 [0.0422–0.0463]	2 (9%)
≥3 to <4 years	24 (12%)	100.0 [97.3–107]	16.0 [14.9–18]	0.0428 [0.0405–0.0431]	3 (13%)
≥4 to <5 years	17 (9%)	105.0 [101–110]	17.5 [16–21]	0.0410 [0.0394–0.0425]	2 (12%)
≥5 to <6 years	23 (12%)	115.0 [110–120]	20.0 [18.5–21.5]	0.0400 [0.0388–0.0413]	1 (4%)
≥6 to <7 years	16 (8%)	116.5 [110–120.5]	23.3 [21.5–26]	0.0371 [0.0352–0.0387]	1 (6%)

Note: Values are numbers or median [1st–3rd quartile].

settings device is key, especially in patients with high surface-area-to-weight ratio; (3) defining high temperature monitor alarm settings at the beginning of the anesthetic could be helpful in detecting iatrogenic hyperthermia.[8] On the contrary, some questions remain unclear: (a) When and to what temperature warming devices should be set? It can be hypothesized that lower initial temperature settings need to be applied when the baseline temperature is already high, such as in febrile patients. Children who combine risk factors for the development of iatrogenic hyperthermia may just need exposure to room temperature. (b) How much has potential noncompliance with our standards by the attending anesthesiologists contributed to excessive warming? Since we did not record the temperature settings over the course of surgery, we cannot accurately quantify this factor. Nevertheless, we followed our standard of care, determined by our standard operating practice. In daily practice, compliance with standard operation procedures is never 100%. Therefore, our

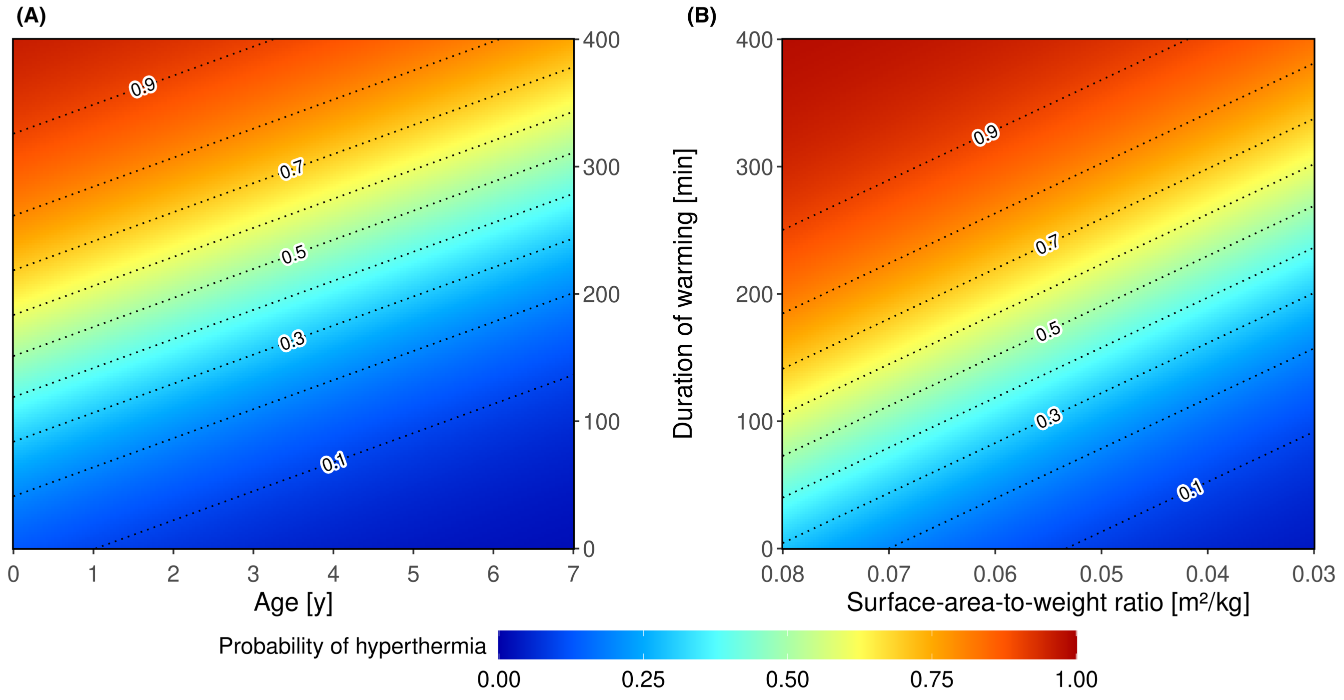

FIGURE 3 Probability of iatrogenic hyperthermia according to a fitted logistic regression model with duration of warming and (A) age or (B) surface-area-to-weight ratio, respectively, as explanatory variables. Blue color denotes low probability and red color high probability. Contour lines (dotted black) show 10%-intervals.

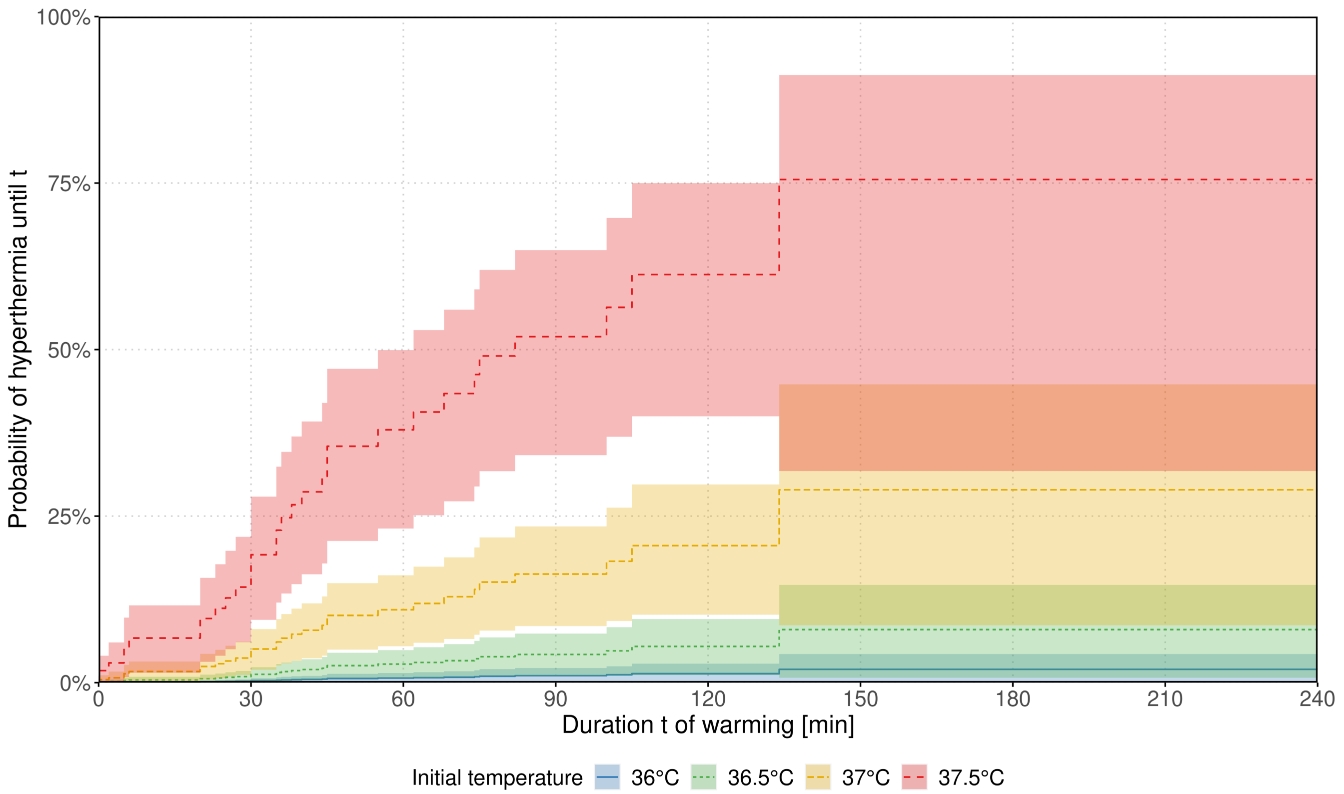

FIGURE 4 Probability of hyperthermia over time in relationship to the baseline temperature (with 95%-CI). The value at time t states the probability of a patient to become hyperthermic with given baseline temperature.

findings probably reflect real-life conditions. Since the delay of core temperature from 37.3°C to the maximum is reached only 113 min later (Figure 2), it is likely that it is much too long to be explained only by redistribution processes inside the body. Therefore, it is plausible that the long delay is at least partially explained by noncompliance to our standard.

This study has further limitations. First, the purpose of our underlying research was to analyze agreements of different measurement methods against standard esophageal core reference. Thus, we neither measured baseline (preoperative) temperatures before prewarming nor did we document changes in temperature settings over the course of surgery, limiting the generalizability of our results. Second, apart from standard of care, we also did not specifically follow up patients who developed hyperthermia or looked for any potential unfavorable outcomes associated with it. Third, it is difficult to compare our results to the daily clinical practice where the recommended 24°C operating room temperature is most likely not achieved.[1] Moreover, as we only utilized underbody blankets, results may differ when upper-body blankets are used. Fourth, it would be a challenging task to extrapolate from our results any conclusions related to the intraoperative temperature management during major abdominal surgery or other surgical procedures where heat loss is more pronounced compared to cases included in the current research.[1] Lastly, no conclusion can be drawn related to the perioperative temperature management of preterm infants and neonates, given the small number available to analyze in the current study. We speculate that the settings that caused excessive warming in older children are just enough to compensate for the greater heat loss in the very young children.

In conclusion, external warming by forced-air needs to be closely monitored and adjusted in a timely manner to avoid iatrogenic hyperthermia in children, especially during long procedures, in young age, and in patients with higher surface-area-to-weight ratio and higher baseline temperature. These risk factors should be routinely considered in pediatric anesthesia to tailor an appropriate warming strategy that is effective in preventing both hypo- and hyper-thermia.

AUTHOR CONTRIBUTIONS

Clemens Miller performed conceptualization, methodology, validation, formal analysis, data curation, investigation, writing—original draft, writing—review and editing, visualization, and project administration. **Anselm Bräuer** performed conceptualization, methodology, writing—review and editing, and supervision. **Johannes Wieditz** performed methodology, formal analysis, data curation, writing—review and editing, and visualization. **Katharina Klose** performed investigation and writing—review and editing. **Carlo Pancaro** performed writing—review and editing. **Marcus Nemeth** performed conceptualization, methodology, validation, formal analysis, data curation, investigation, writing—original draft, writing—review and editing, and project administration.

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CONFLICT OF INTEREST

A. Bräuer is a member of the advisory board of 3 M Europe and received payments from 3 M Germany, 3 M Europe, 3 M Asia Pacific Pte Ltd. Singapore, The Surgical Company Netherlands and Moeck and Moeck GmbH Germany for consultancy work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study is a pooled analysis from two prospective studies, which were approved by the Institutional Review Board of the University Medical Centre Goettingen, Goettingen, Germany (25/1/19 and 22/2/21, respectively).

PATIENT CONSENT STATEMENT

Written informed consent from parents or legal guardians as well as children assent were obtained before enrolment.

CLINICAL TRIAL REGISTRATION

This study is a pooled analysis from two prospective studies, which were registered in the German Clinical Trials Register (DRKS00016655 and DRKS00024703, respectively).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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