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ORIGINAL ARTICLE

Association of response time and intermittent hypoxemia in extremely preterm infants

Sven Martin[1] | Benjamin W. Ackermann[2] | Ulrich H. Thome[2] | Martin Grunwald[1] | Stephanie M. Müller[1]

[1]Haptic Research Lab, Paul Flechsig Institute of Brain Research, University of Leipzig, Leipzig, Germany

[2]Division of Neonatology, University Hospital for Children and Adolescents, Leipzig, Germany

Correspondence
Stephanie M. Müller, Haptic Research Lab, Paul Flechsig Institute of Brain Research, University of Leipzig, Liebigstraße 19, Haus C, 04103 Leipzig, Germany.
Email: s.mueller@medizin.uni-leipzig.de

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Abstract

Aim: To determine the relationship between medical staff's response time (RT) to oxygen saturation (SpO_2) below 80% and the associated time from tactile intervention until SpO_2 normalisation (CT).

Methods: Time-lapse video and continuous SpO_2 were recorded for six consecutive 24 h periods. Regression analyses of RT and SpO_2 in association with postmenstrual age (PMA), weight, infant sex and frequency of intermittent hypoxemia (IH).

Results: Five hundred and twelve hypoxemia episodes received tactile intervention in 20 extremely preterm infants (gestational age ≤28 weeks, birthweight <1500 g). Median RT was 20.5 s (IQR 16.63–25.50). RT increased with increased IH frequency ($p=0.023$) independently of PMA and weight. SpO_2 decreased by 3.7% with every 10 s RT ($p=0.039$). Time until SpO_2 normalisation was strongly associated with RT ($\beta=0.58$, $p=0.042$). The association was amplified by lower PMA ($p=0.043$). Female preterm infants experienced longer RT than males ($p=0.027$). Because the total length of an IH is the sum of RT and CT, preterm infants with low PMA can reach a critical hypoxemia duration of >60 s, even with short RT.

Conclusion: The RT is a critical factor that affects the overall time of IH treatments and the depth of desaturation. The consequences of a prolonged RT are worse for more immature preterm infants.

1 | INTRODUCTION

Apnoea of prematurity (AOP) and associated oxygen desaturation affect 78% of infants born before the completed 28th week of gestation and 84% of infants with a birth weight of under 1000 g in a clinically relevant manner.[1] The administration of methylxanthines and doxapram is an established pharmacological therapy to reduce AOP and the associated hypoxemia.[2–4] A non-pharmacological treatment is the use of respiratory support. Approaches such as continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation (NIPPV) reduce obstructive AOP through increased functional residual capacity (FRC).[2,4,5] Another treatment approach is a

Abbreviations: AOP, Apnoea of prematurity; APGAR, appearance, pulse, grimace, activity, respiration; CI, confidence interval; CPAP, continuous positive airway pressure; CT, completion time; FiO_2, inspiratory oxygen fraction; FRC, functional residual capacity; IH, intermittent hypoxemia; IH_{freq}, relative frequency of intermittent hypoxemia; *IQR*, interquartile range; LL, lower limit of confidence interval; *M*, mean; Mdn, median; NICU, neonatal intensive care unit; NIPPV, non-invasive positive pressure ventilation; PMA, postmenstrual age; RT, response time; SD, standard deviation; SE, standard error; SpO_2, peripheral oxygen saturation; SpO_{2IH}, peripheral oxygen saturation during intermittent hypoxemia; SpO_2min_{RT}, lowest peripheral oxygen saturation during response time; UL, upper limit of confidence interval; W_{SM}, the weight of preterm infants at the start of measurement.

mild increase of oxygen fraction in the respiratory gas, which, however, may increase the risk of retinopathy of prematurity.[2] Despite these treatments, central and mixed apnoea can occur causing intermittent hypoxemia (IH).[4] In the clinical practice of a neonatal intensive care unit (NICU), the patient monitoring system informs the medical staff about acute IH. An optical and acoustic alarm occurs if the oxygen saturation (SpO_2) falls below a preset threshold. If a central apnoea is identified, the use of tactile stimulation is the most established non-pharmacologic intervention procedure.[6–8] Further intensive medical interventions must be initiated if tactile stimulation does not restore spontaneous breathing.

Especially, IH <80% SpO_2 that last longer than 60 s have an increased risk of negatively affecting neurological and motor development.[9] Moreover, IH is associated with a higher clinical risk of intraventricular haemorrhage, retinopathy of prematurity, bronchopulmonary dysplasia and neurological impairment.[10,11]

The alarms most commonly encountered in a NICU are desaturation alarms.[12] The increasing number of alarm-generating medical devices in NICUs worldwide leads to increased workloads for medical staff.[13] Not all of these alarms require direct intervention.[12] One consequence of a smaller proportion of relevant alarms compared to the total number of alarms is longer response times (RT) of medical staff.[14] This phenomenon is known as 'alarm fatigue'.[15] Other factors might also influence RT, for example, patient sex is an important factor in many physiological and pathological processes.[16] The mortality rate is higher in male than female infants.[17] Furthermore, many cardiopulmonary and neurological comorbidities (e.g. bronchopulmonary dysplasia, intraventricular haemorrhage, respiratory distress syndrome) show significant sex differences, as well as prenatally surfactant is produced in females earlier in gestation.[17] Male infants between 32 and 35 weeks of postmenstrual age (PMA) showed a significantly higher incidence of desaturations and bradycardia than female infants.[18] A later study by the same authors found a non-significant 18% higher incidence of IH in male infants.[16]

To the best of our knowledge, no study exists that examined the effect of medical staff's RT on the desaturation of IH and time until SpO_2 normalisation.

Hypothesis 1a. Since high frequencies of desaturation alarms can potentially lead to alarm fatigue,[13] a linear increase in medical staff's median RT is expected with higher relative IH frequency (IH_{freq}).

Hypothesis 1b. Assuming that male preterm infants show more IH than female preterm infants[18] and that higher IH_{freq} leads to longer median RT, we expect significantly longer median RT in male preterm infants.

Hypothesis 2a. Preterm infants with recurrent apnoeas have lower FRC and desaturate twice as fast as preterm infants with rare apnoea events.[19] Furthermore, an exploratory analysis ($N=4$ preterm infants) indicated a correlative relationship between the delay of treatment onset and the depth of saturation decline.[20] However, the extent of this correlation remains unknown. With this in mind, we expect a linear decrease in oxygen saturation with longer median RT when an IH with SpO_2 below 80% has occurred.

Hypothesis 2b. One study indicated that the recovery from apnoea-inducted desaturation took twice as long as the saturation drop after apnoea onset.[21] Thus, we expect a positive linear association of completion time (CT; time from the onset of a tactile intervention until recovery of SpO_2 >80%) and median RT (Figure S1).

Key Notes

- A higher frequency of intermittent hypoxemia is associated with a delayed response time (RT) of medical professionals.
- A longer RT to acute hypoxemia is associated with a lower level of oxygen saturation and a longer time until SpO_2 normalisation.
- The consequence of a longer RT for hypoxemia with oxygen saturation below 80% is worse for infants with lower postmenstrual age.

2 | METHODS

2.1 | Participants

Study participants were recruited from September 2019 to November 2020 at a tertiary care neonatal department (Germany) after parents were informed and parental consent was given. Extremely preterm infants with a gestational age <28 weeks, a birthweight <1500 g and a postnatal age between 1 and 6 weeks were eligible, if they received non-invasive or no respiratory support and exhibited IH. All preterm infants with severe diseases (e.g. sepsis), chromosomal anomalies and malformations requiring surgical correction, or receiving invasive respiratory support were excluded. Applying these strict criteria to the screening procedure created a very homogenous group of participants.

2.2 | Study design

The study was planned and conducted according to the ethical principles of the World Medical Association Declaration of Helsinki and has been reviewed and approved in advance by the Ethics Committee of the University of Leipzig (265/18-EK). This study followed the STROBE reporting guidelines and was registered under DRKS00018085.

2.3 | Video and data recording

The time-lapse camera TLC200Pro from Brinno was used to record the video data. The cameras were attached to the incubator cover (Giraffe, GE Healthcare) with a suction cup. The camera recorded one image per second even in low ambient light. No sound was recorded. The study period was six consecutive days per preterm infant. Every 24 h, the camera was replaced for video readout and battery charging. The system time of the camera was set manually at each camera change using a radio-controlled clock.

Physiological data were measured in all participants using the IntelliVue MX700 patient monitor system (Philips Healthcare) equipped with the SpO_2 sensor RD-Set (Masimo Corp.). In three infants, oxygen saturation was measured using the Radical-7 pulse oximeter (Masimo Corp) with the LNCS Neo SpO_2-sensor (Masimo Corp). The patient monitor system was coupled with a Sophie ventilator (Fritz Stephan GmbH), which provided non-invasive respiratory support and also recorded the physiologic data on an internal memory card. The latter was enabled by a software update of the ventilators, kindly provided by Fritz Stephan GmbH. The recording rate of physiological data was one measurement value every 2 s. During routine ventilator changes, the memory cards were read out. A radio-controlled clock was used to synchronise the ventilator with the time-lapse cameras. A change and reset of the inspiratory oxygen fraction (FiO_2) alarm limit of 1% was used to mark the exact camera change time in the recorded data.

2.4 | Data pre-processing

After data collection was finished, video data and physiological data were merged. For this purpose, the software 'Timelapse' developed by Sven Martin (Haptics Research Laboratory, Medical Faculty of the University of Leipzig, Germany) was used. The Timelapse software was programmed in VB.net 2015 and used OpenCV open-source program library to integrate the video files (Figure S2). All calculations of the Timelapse software were empirically tested and evaluated on randomly chosen samples by KB, WA and SM.

The software enabled automatic, criteria-based detection of IH. An IH was defined as SpO_2 below 80% for at least 10 s. The 80% threshold was derived from the critical alarm limit set as default on the MX700 monitor system. Two of the 20 participants had a slightly different limit of 84% and 82% at the beginning of the measurement. During the study period, those limits were adjusted to 82% and 80% respectively. The critical alarm limit average across all participants was 80.30%. Furthermore, the critical oxygen threshold of 80% corresponds with the apnoea scoring system by Poets.[22] Exceeding the 80% threshold indicates the end of the detected IH. If the saturation fell again below the critical threshold within 10 s after exceeding it, the episode was added to the already detected one. To check if a detected IH event is a valid representation of a critical alarm event, we determine the delay of a MX700 between the SpO_2 value falling below the critical limit and the red alert occurrence based on video observations. We measured a delay of 3 s between events and alerts. Missing values and zeros were excluded. Only valid oxygen saturation values were used for the automated detection of IH.

Three independent raters viewed the video footage and marked the rest phases and the tactile intervention during IH. Rest phases were all periods in which the preterm infants lay in the incubator and no action was performed. Only IH during rest were included in analyses to ensure differentiability between tactile intervention for IH, sensor shifts and manual healthcare. Furthermore, we focused on rest phases because IH frequency can be influenced by external stimuli, such as healthcare.[23,24] Only those actions were marked as tactile intervention if they were performed by medical professionals, if manual contact occurred after IH began and if IH occurred during rest. The start of a tactile intervention was defined as the first visible physical contact of a medical professional and the preterm infant. The end of a tactile intervention was the time of the visible release of the last physical contact. A series of multiple physical contacts were added together if they were less than 10 s apart. Tactile intervention sequences with additional medical or nursing actions were excluded from analyses because cause and effect could not be distinguished in time-lapse footage.

The relative IH frequency during rest (IH_{freq}) was calculated by dividing the total number of IH during the rest phases by the duration of all rest phases of a preterm infant. Because RT, CT and the associated SpO_2 values were not normally distributed, the median RT and median CT values for each preterm infant were calculated. The median values of oxygen saturations during IH (SpO_{2IH}) and lowest oxygen saturation during RT (SpO_2min_{RT}) were calculated analogously. PMA and weight of preterm infants at the start of measurement (W_{SM}) were used for all regression analyses as potential covariates. The PMA was calculated from the first day of the last menstrual period until birth, plus the postnatal age of the preterm infant at the start of measurement.

2.5 | Statistics

The program SPSS 27 (IBM Corp.) was used for statistical analyses. The significance level was set at $\alpha = 5\%$. Mann–Whitney-*U* test was used for group comparison of sex effects. To analyse the associations between IH_{freq}, CT, SpO_2min_{RT} and RT, linear regressions with backward elimination were calculated. A significance value of $p > 0.100$ was set as the exclusion criteria for regression models. Statistical assumptions for the regression analyses were met. For linear regression analysis with one predictor a sample size of $N = 20$ was calculated using G*Power version 3.1.9.7, expecting large effect sizes $R^2 = 0.26$ with a power of $(1 - \beta) = 0.70$ even thou smaller effects might be missed.[25,26]

3 | RESULTS

Twenty preterm infants (10f/10m) participated in the study (Figure 1). The preterm infants' chronological age at the measurement's beginning

ranged from 11 to 37 days after delivery. All of the preterm infants received respiratory support. Twelve of the preterm infants received CPAP, and eight preterm infants received NIPPV. The ventilator's automatic FiO_2 adjustment (closed loop control of inspired oxygen) function was used in 13 preterm infants. All participants received enteral caffeine base administration of 3–8 mg/kg/day (*Mdn* = 7.00; IQR = 5.00–7.00) methylxanthine. All preterm infants in this study received skin-to-skin contact in the form of Kangaroo-Care (*Mdn* = 1.44 h/day; IQR = 1.08–2.09). Throughout the study period, 70 paediatric nurses (67 female) of whom 29 nurses (41%) had advanced special training in anaesthesia and critical care, treated the participating preterm infants. They had a mean age of *M* = 37.12 years (*Mdn* = 35.00; IQR = 26.75–47.25) and a mean professional experience of *M* = 14.03 years (*Mdn* = 9.00; IQR = 2.00–25.25). All nurses worked in a three-shift system consisting of early shift (6:00 AM–2:00 PM), late shift (2:00 PM–10:00 PM) and night shift (10:00 PM–6:00 AM). The clinical characteristics of the preterm infants are shown in Table 1. Male and female preterm infants did not differ in their clinical parameters. Data were recorded on six consecutive days per infant. Thus, the median of the measurement period was 142.00 h (IQR = 140.00–143.00). The percentage of valid data was 98.85% (IQR = 98.62–99.22) for the SpO_2 values.

In all, 2691 IH (64.76% of total IH) occurred with SpO_2 below 80% for more than 10 s during the rest phases. Rest phases accounted for the majority (78.9%) of the total measurement time. The median duration of the rest phases was 114.60 h (IQR = 110.53–118.64) per preterm infant. Per preterm infant, a median of 124.50 IH (IQR = 58.25–202.00) occurred during rest phases. Tactile interventions were observed during 512 IH (19%). Per preterm infant, a median of 19.50 (IQR = 8.75–35.00) of IH were treated with tactile interventions. There was no significant difference between early, late and night shifts in terms of IH_{freq}, RT and CT. The results of the descriptive data analysis are reported in Table 2.

3.1 | Hypothesis 1a: Hypoxemia frequency and RT

To test whether there was an association between IH_{freq} and medical staff's RT, a linear regression analysis with backward elimination (model M1) was performed. The regression model explained 26% of the variance, $R^2 = 0.26$, F (1, 18) = 6.19, $p = 0.023$. The level of IH_{freq} predicted a significant increase in median RT, $\beta = 3.95$, $t = 2.49$, $p = 0.023$. PMA and W_{SM} did not significantly affect the model and were therefore excluded. Figure 2A shows a graphical representation. Full details are provided in Table S1.

3.2 | Hypothesis 1b: The effect of infants' sex on median apnoea frequency and median RT

The hypothesis that male preterm infants have longer median RT because of higher IH_{freq} could only be tested to a limited extend. The comparison of male and female preterm infants concerning IH_{freq} did not differ significantly. Nevertheless, there was a significant sex effect of median RT ($Z = -2.19$, $p = 0.027$, $d_{Cohen} = 1.12$). The descriptive data analysis showed longer RT for female infants (see Table 3 and Figure 2B).

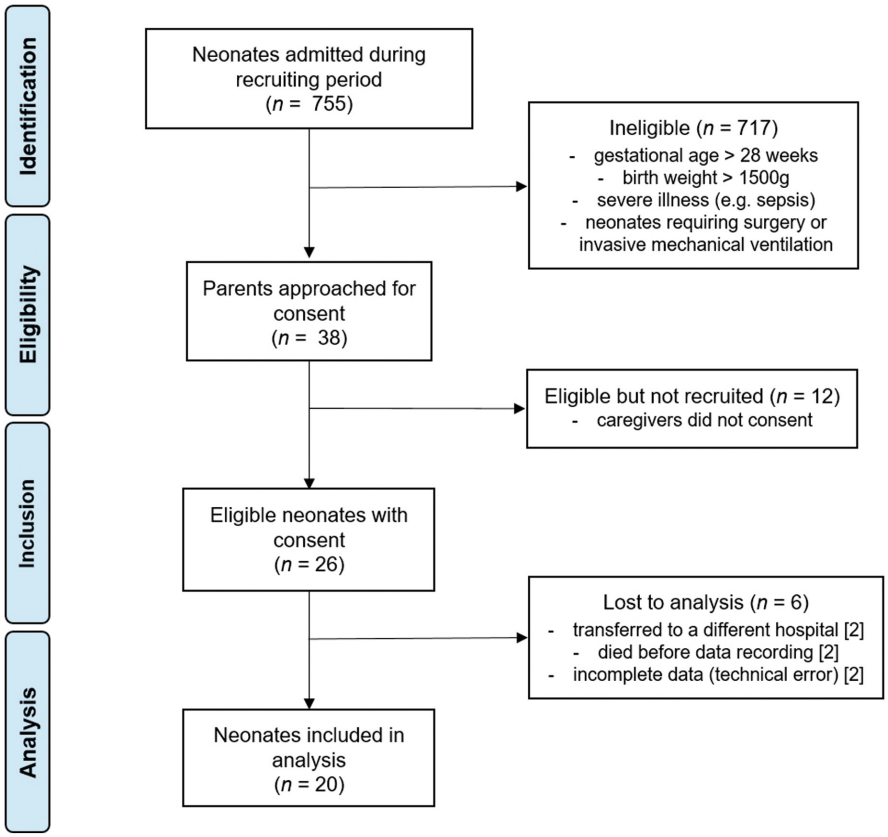

FIGURE 1 STROBE flow diagram.

TABLE 1 Clinical description of participants.

Information about the participants	Number of participants				
	Male ($n=10$)	Female ($n=10$)	*Z*-value	*p*-value	d_{Cohen}
Information about the mother					
Age of mother (years)	*Mdn* = 33.50 (IQR = 29.50–38.00)	*Mdn* = 33.00 (IQR = 28.75–39.00)	−0.27	0.809	0.12
	M = 32.90 (SD = 5.67)	*M* = 33.00 (SD = 5.87)			
Caesarean section	10	8			
Infants at birth					
Birth weight (g)	*Mdn* = 905.00 (IQR = 778.75–992.00)	*Mdn* = 722.50 (IQR = 627.50–895.00)	−1.66	0.105	0.80
	M = 861.80 (SD = 186.91)	*M* = 736.00 (SD = 157.16)			
Gestational age (days)	*Mdn* = 183.00 (IQR = 180.25–190.25)	*Mdn* = 177.00 (IQR = 172.25–185.00)	−1.52	0.137	0.72
	M = 183.00 (SD = 6.71)	*M* = 178.10 (SD = 9.28)			
Apgar score at 5 min	*Mdn* = 7.50 (IQR = 6.75–8.00)	*Mdn* = 7.50 (IQR = 7.00–8.00)	−0.37	0.784	0.17
	M = 7.20 (SD = 1.03)	*M* = 7.40 (SD = 1.08)			
Apgar score at 10 min	*Mdn* = 8.00 (IQR = 7.00–8.00)	*Mdn* = 8.50 (IQR = 7.00–9.00)	−1.53	0.191	0.73
	M = 7.60 (SD = 0.70)	*M* = 8.20 (SD = 0.92)			
Doxapram	–	2			
Theophylline	1	–			
CPAP	7	5			
NIPPV	3	5			
Infants at start of measurement					
PMA (days)	*Mdn* = 207.00 (IQR = 201.00–218.50)	*Mdn* = 198.50 (IQR = 189.50–208.00)	−1.48	0.143	0.70
	M = 208.30 (SD = 9.52)	*M* = 200.20 (SD = 13.87)			
W_{SM} [g]	*Mdn* = 1095.00 (IQR = 968.75–1315.00)	*Mdn* = 1020.00 (IQR = 773.75–1082.50)	−1.82	0.072	0.89
	M = 1112.50 (SD = 226.46)	*M* = 938.50 (SD = 229.83)			

Abbreviations: Apgar, appearance, pulse, grimace, activity, respiration; CPAP, continuous positive airway pressure; d_{Cohen}, effect size; IQR, interquartile range; *M*, mean; *Mdn*, median; NIPPV, non-invasive positive pressure ventilation; PMA, postmenstrual age at the beginning of the measurement; *p*-value, statistical significance value; *SD*, standard deviation; W_{SM}, weight at measurement begin; *Z*-value, standardised test value.

3.3 | Hypothesis 2a: RT and desaturation

The relationship between RT and the median oxygen saturation decrease during RT (SpO_2min_{RT}) was analysed with a linear regression analysis with backward elimination (model M2). The result explained 22% of the variance, $R^2 = 0.22$, $F(1, 18) = 4.96$, $p = 0.039$. Duration of RT predicted a significant decrease in SpO_2min_{RT} values, $\beta = -0.37$, $t = -2.23$, $p = 0.039$. PMA and W_{SM} had no significant effect on the model and were therefore excluded. Figure 2C shows a graphical representation. Full details are provided in Table S1.

3.4 | Hypothesis 2b: RT and completion time

The linear regression analysis examined the relationship between the median RT and the median CT (model M3). The regression analysis with backward elimination explained 44% of the variance, $R^2 = 0.44$, $F(2, 17) = 6.73$, $p = 0.007$. The median duration of RT predicted a significant increase in the median CT, $\beta = 0.58$, $t = 2.21$, $p = 0.042$. The PMA had an opposite effect and predicted a significant decrease in the median CT with increasing PMA, $\beta = -0.33$, $t = -2.19$, $p = 0.043$. W_{SM} had no significant effect on the median CT and was excluded. Figure 2D shows a graphical representation. Full details are provided in Table S1.

4 | DISCUSSION

This study investigated the effect of medical staff's RT to preterm infants' IH with SpO_2 below 80% on the amount of saturation drop and time until SpO_2 normalisation.

Hypothesis 1a: We found a significant positive relationship between IH_{freq} and RT. The RT of the medical staff tended to be shorter when the IH_{freq} of a preterm infant was low. The PMA and

Variable	*M*	*SD*	*Mdn*	*IQR*
IH_{freq} (IH/h)	1.24	0.90	1.10	0.52–2.04
RT (s)	20.83	7.04	20.50	16.63–25.50
CT (s)	20.43	9.88	18.25	12.75–25.88
Duration of treated IH during rest (s)	50.23	19.72	48.00	37.63–59.50
SpO_2min_{RT} (%)	69.55	5.64	69.25	65.00–74.25
SpO_{2IH} (%)	74.33	3.60	74.13	72.00–76.88

TABLE 2 Descriptive data analysis of predictor and criterion variables.

Note: All data on IH refer to the rest phases.

Abbreviations: CT, median completion time in seconds; IH, intermittent hypoxemia; IH_{freq}, relative occurrence frequency of IH during rest phases; IQR, interquartile range; *M*, mean; *Mdn*, median; RT, median response time in seconds; *SD*, standard deviation; SpO_{2IH}, median oxygen saturation during IH; SpO_2min_{RT}, a median of the lowest oxygen saturation values during RT.

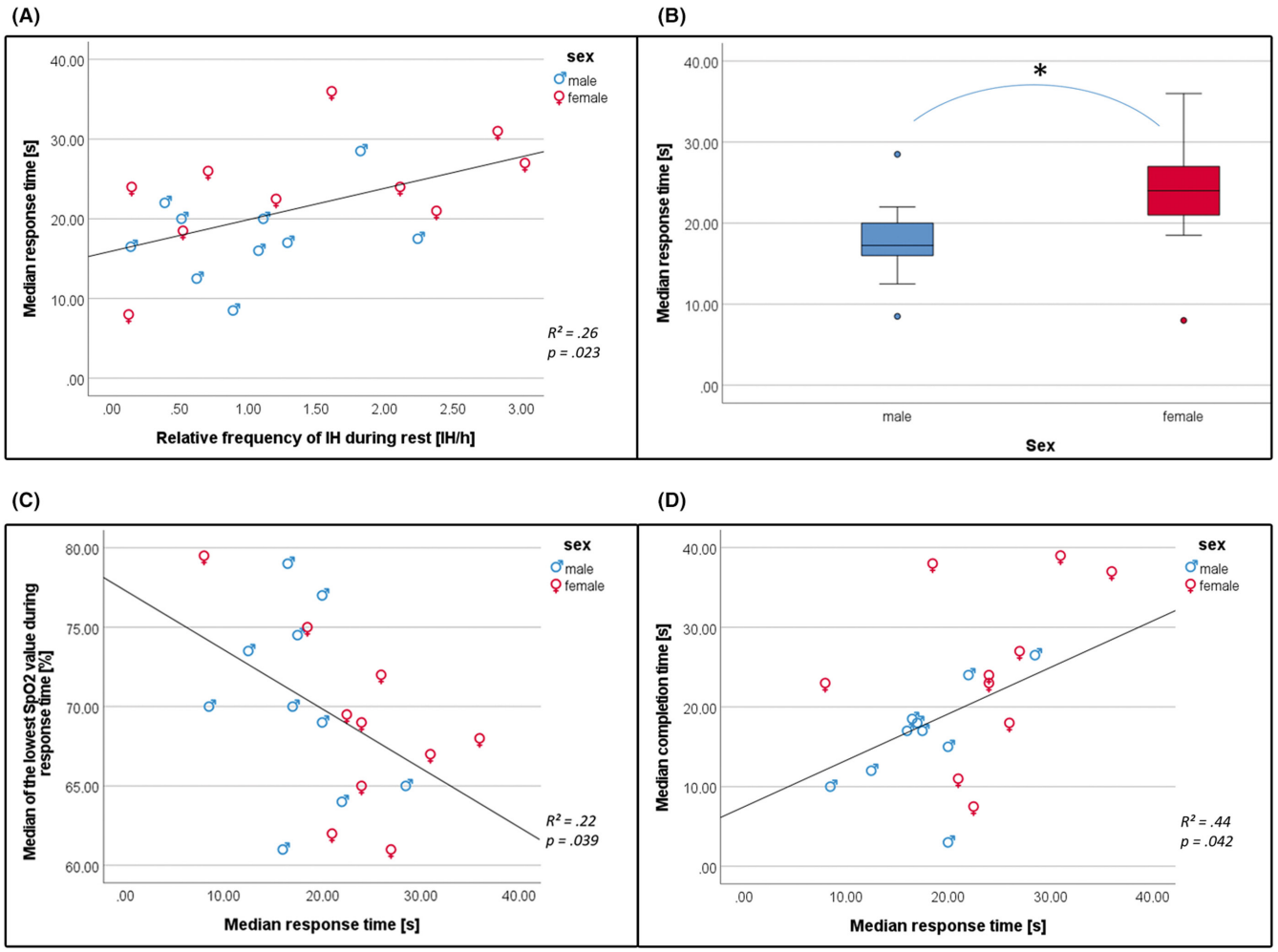

FIGURE 2 (A) Scatter plot with regression line (model M1) of relative hypoxemia frequency (IH_{freq}) and median RT in seconds. (B) Boxplot of median RT (in seconds) of the medical staff during the tactile intervention of IH during rest phases of male and female preterm infants. Asterisk—significant at the $p < 0.05$ level. (C) Scatter plot with regression line (model M2) of the median values of the lowest oxygen saturation during RT (SpO_2min_{RT}) and the median RT in seconds. (D) Scatter plot with regression line (model M3) of median RT in seconds and median completion time in seconds for the group median of the PMA (*Mdn* = 207 days). Descriptively, female preterm infants are shown in red, and male preterm infants are shown in blue.

W_{SM} did not affect the association between IH_{freq} and RT in our sample. The result supports the initial hypothesis that a higher frequency of desaturations may lead to longer RT. It should be taken into account that the majority (65%) of the preterm infants in our study received respiratory support with closed-loop control of inspired oxygen which is associated with an increase in the time

TABLE 3 Descriptive data of male and female preterm infants.

Variable	Male	Female	*Z*-value	*p*-value	d_{Cohen}
RT (s)	*Mdn* = 17.25 (IQR = 15.13–20.50)	*Mdn* = 24.00 (IQR = 20.38–28.00)	−2.19	0.027	1.12
	M = 17.85 (SD = 5.40)	*M* = 23.80 (SD = 7.48)			
IH_{freq} (IH/h)	*Mdn* = 0.99 (IQR 0.48–1.42)	*Mdn* = 1.41 (IQR = 0.43–2.49)	−0.91	0.393	0.42
	M = 1.01 (SD = 0.65)	*M* = 1.47 (SD = 1.09)			
SpO_{2IH} (%)	*Mdn* = 74.38 (IQR = 72.75–77.88)	*Mdn* = 73.50 (IQR = 70.75–76.13)	−1.06	0.305	0.49
	M = 75.18 (SD = 2.93)	*M* = 73.48 (SD = 4.15)			
Duration of tactile intervention (s)	*Mdn* = 43.50 (IQR = 72.75–77.88)	*Mdn* = 53.00 (IQR = 39.38–77.00)	−1.40	0.086	0.66
	M = 42.70 (SD = 14.01)	*M* = 57.75 (SD = 22–34)			

Abbreviations: d_{Cohen}, effect size; IH, intermittent hypoxemia; IH_{freq}, relative occurrence frequency of IH during rest phases; IQR, interquartile range; *M*, mean; *Mdn*, median; *p*-value, statistical significance value; RT, median response time in seconds; *SD*, standard deviation; SpO_{2IH}, median oxygen saturation during IH; *Z*-value, standardised test value.

of SpO_2 spent within the target range, and a decrease in manual interventions in literature.[27,28] The application of close-loop control of inspired oxygen may also reduce the severity and the occurrence frequency of critical IH,[29] however, this association requires further investigations.[30,31]

The presented results strengthen the findings of an earlier study that showed the association between RT and the number of non-actionable alarms.[32] Whether 'alarm fatigue' is the cause of the observed effect cannot be answered. Alarm desensitisation effects are multifactorial and should be investigated in future studies explicitly.[14]

Hypothesis 1b: IH_{freq} was statistically equal in both sexes. However, contrary to expectations we found a non-significant trend towards higher IH_{freq} in female infants in the present study. This contradicts other findings of higher desaturation incidence in male infants.[16,18] Therefore, the expected sex effect regarding RT could not be confirmed according to the hypothesis. Instead, female preterm infants showed significantly longer RT (*Mdn* = 24.00 s) than male preterm infants (*Mdn* = 17.25 s). This difference may reflect the tendentially higher IH frequency in female infants in our sample. The effect is in line with the results of hypothesis 1a. Additionally, the higher mortality rate and the perceived higher health risk profile of male preterm infants may be factors influencing RT.[33,34]

The results of a study in 2017 suggest that medical staff prioritise response behaviours for more vulnerable preterm infants.[35] Whether the present result indicate a heuristic response of the medical staff to the potentially more vulnerable group can only be speculated. If the sex of preterm infants has a direct or indirect influence on the heuristics of the medical staff and their response behaviour to alarm events needs to be investigated in further studies. Desaturation speed could be another possible explanation for the observed sex-specific effect. If nurses already reacted to the non-critical alarm and one group had a faster saturation decrease, they would reach the critical SpO_2 threshold sooner, which leads to longer RT, given the same start condition. Future studies need to clarify whether there is a sex-specific difference in desaturation speed.

Hypothesis 2a: As expected, a significant, negative association between RT and SpO_2min_{RT} was observed. PMA and W_{SM} had no significant effect on the regression model. With every 10 s delay of tactile intervention, a further median saturation drop of 3.7% occurred. This result adds a quantitative measure to a previously shown correlative relationship.[20] It should be emphasised that in our study, only those IH with oxygen saturation below 80% were analysed. Therefore, further desaturations are critical, and it remains unknown how long suboptimal saturations persisted before reaching critical levels. The FRC provides a buffer to stabilise oxygenation during brief IH.[22] Smaller remaining FRC of preterm infants leads to faster SpO_2 drops during breathing interruptions.[19] This is particularly important in periodic apnoeas since oxygen saturation drops twice as fast as during single apnoea events.[3] This underscores the importance of prompt action during acute IH of a preterm infant.

Hypothesis 2b: We found a significant, positive association of RT and CT. A delayed treatment start resulted in slower saturation recovery to a noncritical value. PMA influenced this association. Consequently, a longer RT had a stronger impact on younger preterm infants than on older ones. For example, in a preterm infant with a PMA of 182 days, an RT increase of 10 s resulted in a CT increase of 21.57 s. In comparison, a preterm infant with a PMA of 230 days, a RT increase of 10 s resulted in a CT increase of 5.63 s. Because the total length of an IH is the sum of RT and CT, preterm infants with low PMA can reach critical hypoxemia durations of >60 s, even with short RT. Future studies on treatment times of IH should consider the PMA. The W_{SM} had no significant effect on CT. The observed relationship between RT and CT is consistent with hypothesis 2a. Longer RT resulted in a more profound saturation drop, which resulted in longer CT of an IH treatment. Accordingly, the median RT of the medical staff influences the median treatment time of an IH. The consequences of repeated prolonged IH range from a more extended hospital stay to an increased risk of neurological, cognitive and motor developmental delays as long-term consequences.[9,18] However, the duration of treatment for IH may also depend on other influencing factors. Examples include the high variance of tactile-treatment procedures for acute IH.[6,8] In addition, it is currently unknown how sensitively premature infants react to the intensity of tactile stimuli. These aspects of the treatment of IH need to be clarified in future studies.

5 | LIMITATIONS

One limitation is the small study sample. However, medium to large effect sizes even in this small but homogenous sample indicate robust results. Another limitation is the unknown walking distance between the nursing station and the incubators. Future studies should investigate if RT can be reduced by positioning vulnerable infants closer to the nursing station. It is also unknown if the professional experience of the nurses affect their RT to critical alarms in a positive or negative manner. Future studies need to clarify if perhaps unexperienced nurses show longer RT or if perhaps experienced nurses show some kind of 'burn-out' effect. Additionally, the usage of cameras is always at risk for Hawthorne effects. However, we expected a minimal behavioural adjustment of the medical staff due to the long study period and the high incidence of experimental studies conducted in the NICU.

6 | CONCLUSION

In terms of tactile IH interventions, longer RT affects the depth of saturation decline and leads to longer overall treatment durations. The consequences of prolonged RT are even worse for immature preterm infants and those with higher IH_{freq}. The presented work provides empirical evidence for the direct effect of RT on the duration of hypoxemia.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interests.

DATA AVAILABILITY STATEMENT

Data are available on request.

ORCID

Sven Martin https://orcid.org/0000-0001-6488-1714

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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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