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ABSTRACT

Objective Application of a face mask may provoke the trigeminocardiac reflex, leading to apnoea and bradycardia. This study investigates whether re-application of a face mask in preterm infants at birth alters the risk of apnoea compared with the initial application, and identify factors that influence this risk.

Methods Resuscitation videos and respiratory function monitor data collected from preterm infants <30 weeks gestation between 2018 and 2020 were reviewed. Breathing and heart rate before and after the initial and subsequent mask applications were analysed.

Results In total, 111 infants were included with 404 mask applications (102 initial and 302 subsequent mask applications). In 254/404 (63%) applications, infants were breathing prior to mask application, followed by apnoea after 67/254 (26%) mask applications. Apnoea and bradycardia occurred significantly more often after the initial mask application compared with subsequent applications (apnoea initial: 32/67 (48%) and subsequent: 44/187 (24%), p<0.001; bradycardia initial: 61% and subsequent 21%, p<0.001). Apnoea was followed by bradycardia in 73% and 71% of the initial and subsequent mask applications, respectively (p=0.607).

In a logistic regression model, a lower breathing rate (OR 0.908 (95% CI 0.847 to 0.974), p=0.007) and heart rate (OR 0.935 (95% CI 0.901 to 0.970), p<0.001) prior to mask application were associated with an increased likelihood of becoming apnoeic following subsequent mask applications.

Conclusion In preterm infants at birth, apnoea and bradycardia occurs more often after an initial mask application than subsequent applications, with lower heart and breathing rates increasing the risk of apnoea in subsequent applications.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Application of a face mask may provoke the trigeminocardiac reflex, leading to apnoea and bradycardia.
⇒ Apnoea occurs in 54% of preterm infants ≤32 weeks after initial face mask placement at birth.
⇒ In term and late preterm infants, apnoea occurs more often after initial compared with subsequent mask applications (29% vs 8%).

WHAT THIS STUDY ADDS

⇒ Apnoea and bradycardia occurs more often after an initial mask application than subsequent applications in preterm infants, with lower heart and breathing rates increasing the risk of apnoea in subsequent applications.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study will form the rationale for further studies investigating possible mechanisms to avoid inducing apnoea and bradycardia after face mask application, which might be provoked by the trigeminocardiac reflex.

INTRODUCTION

To support spontaneous breathing after birth, non-invasive respiratory support is often provided via a face mask. However, applying a face mask at birth might stimulate the rapidly adapting cutaneous receptors of all three branches of the trigeminal nerve, thereby provoking the trigeminocardiac reflex (TCR) resulting in apnoea and a reduction in heart rate (HR).[1–6] Recently, we have shown that apnoea occurred in 54% of preterm infants ≤32 weeks after initial face mask placement at birth, often followed by bradycardia.[2]

When mask ventilation is not effective, resuscitation guidelines primarily recommend MRSOPA (mask adjustment, reposition airway, suction mouth and/or nose, open mouth, pressure increase and alternative airway), to improve mask seal and/or resolve airway obstruction.[7 8] A recent study in term and late-preterm infants demonstrated that apnoea was more frequently observed after initial mask application when compared with subsequent mask applications.[9] They suggested that repeated or prolonged stimulation of the trigeminal nerve could lead to habituation and thus a diminished TCR response during subsequent mask applications.[10] Although this response was evident in term and late-term infants, it is not known whether it also occurs in very preterm infants as some neural circuits are not fully developed by the time of preterm birth.[1] Our aim was to investigate whether re-applying a face mask (ie, subsequent mask application) alters the risk of inducing apnoea compared with the initial application, in preterm infants <30 weeks during the first 10 min of respiratory support after birth. We also aimed to identify factors that may alter the risk of inducing apnoea during mask re-applications.

METHODS

A retrospective study was performed at the Leiden University Medical Centre. All available resuscitation videos and respiratory function monitor

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recordings of preterm infants <30 weeks of gestation recorded between 2019 and 2020 were included. Recordings were excluded if (i) there were congenital malformations affecting the cardiopulmonary transition or (ii) when data were incomplete or unreliable.

A face mask (Neonatal Resuscitation Mask, Fisher & Paykel Healthcare, Auckland, New Zealand) and Neopuff Infant Resuscitator (Fisher & Paykel Healthcare) were used to provide non-invasive respiratory support at birth. All gases were heated and humidified. A disposable flow sensor (Avea Varflex Flow transduser; Carefusion, California, USA) was placed in between the face mask and the T-piece to record respiratory function using the New Life Box (Advanced Life Diagnostics, Weener, Germany) and Polybench physiological software (Applied Biosignals, Weener, Germany). HR and oxygen saturation (SpO_2) were recorded by a Radical-7 Masimo SET pulse oximeter probe (Masimo, California, USA) placed around the infant's right hand. Breathing parameters were calculated via a breath-by-breath analysis using Pulmochart software (Applied Biosignals).

Resuscitation recordings and respiratory function data were reviewed by two researchers (AH/KLAMK). All initial applications and subsequent face mask applications, irrespective of the time interval between applications, were reviewed. Subsequent applications were defined as a repositioning or re-application of the face mask, which involved both the full or partial removal of the face mask, followed by re-application. Spontaneous breathing was determined by using the flow waveforms, or if not available (eg, before initial application or during repositioning) observations from the video recording. These indicators of breathing included visible chest excursions, crying or vivid movements of the extremities. Apnoea was defined as the absence of spontaneous breathing for at least 5 s. In addition, physiological parameters were assessed 20 s before and 30 s after face mask (re-) application. A reduction in HR was defined as a decrease of >10 beats per minute (bpm), bradycardia as a HR <100 bpm and hypoxia as SpO_2<80%. Other outcomes assessed by resuscitation recordings were the occurrence of tactile stimulation, suctioning or intubation. To describe baseline characteristic, the following patient characteristic were collected from the medical records: gestational age, birth weight, gender, Apgar score at 1 and 5 min, mode of delivery, use of corticosteroids, umbilical cord blood pH, multiple birth and type of anaesthesia.

All data were analysed using IBM SPSS Statistics V.25 (IBM, Chicago, Illinois, USA, 2021). Dichotomous data were presented as number (%) and analysed using the χ^2 test or Fisher's exact test. Continuous parametric data were tested for normality and were presented as mean±SD and analysed with the independent sample t-test. Non-parametric data were analysed using a Mann-Whitney U test or Wilcoxon signed rank test and presented as median (IQR). A logistic regression was used to predict the occurrence of apnoea after subsequent mask application by using the mean variables tidal volume, breathing rate, minute volume, HR and SpO_2 in the 20 s before application of the face mask. A p value <0.05 was considered statistically significant.

RESULTS

Of the 119 eligible infants, 111 infants (median gestational age of 28^{+0} (26^{+0}–29^{+1}) weeks) were included in this study. In total, 404 mask applications (102 initial and 302 subsequent mask applications) were observed with a median of 3 (2–5) applications per infant (figure 1, table 1).

Effect of mask application on spontaneous breathing

In 63% (254/404) of applications, spontaneous breathing was present before mask application and in 30% (76/254) of these applications, the mask application was followed by apnoea (figure 1). Apnoea occurred significantly more often after the initial than subsequent applications (initial: 32/67 (48%) vs subsequent: 44/187 (24%), p<0.001). However, neither the

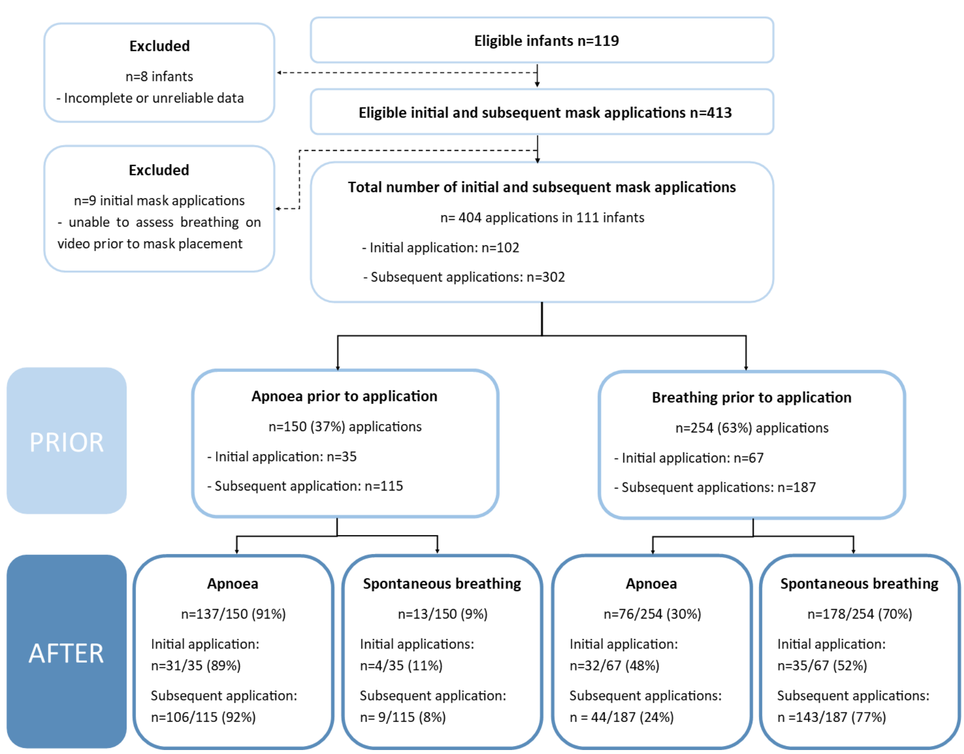

Figure 1 Flow chart.

Table 1 Patient characteristics

	All infants (n=111)
Gestational age (weeks), median (IQR)	28^{+0} (26^{+0}–29^{+1})
Birth weight (g), mean±SD	1026 ± 286
Males, n (%)	56 (51)
Multiple birth, n (%)	53 (48)
Antenatal corticosteroids complete, n (%)	76 (69)
Caesarean delivery, n (%)	53 (48)
General anaesthesia, n (%)	10 (9)
Apgar score 1 min, median (IQR)	5 (3–7)
Apgar score 5 min, median (IQR)	8 (6–9)
Umbilical cord blood pH, mean±SD	7.26 ± 0.13*
CPAP level (cm H_2O), median (IQR)	7.1 (6.3–7.7)
SI given, n (%)	77 (69)
PPV given, n (%)	66 (60)
Intubation, n (%)	19 (16)
Number of mask repositions, median (IQR)	3 (2–5)

*Twenty-nine (26%) missing measurements.
CPAP, continuous positive airway pressure; PPV, positive pressure ventilation; SI, sustained inflations.

median time for apnoea onset after mask placement (6.9 (2.0–16.3) vs 5.9 (0.43–14.9) s, p=0.597) nor the duration of apnoea (20.2 (9.4–31.2) vs 19.0 (9.5–46.2) s, p=0.375) were different between the initial and subsequent applications (table 2).

In 30 infants that were apnoeic prior to mask repositioning, breathing could be assessed on video during the reposition and/or re-application. Of these, 13/30 (43%) started to breathe spontaneously when the mask was temporarily removed. However, most of these infants 11/13 (84%) became apnoeic again when the mask was re-applied to the infant's face.

Effect of mask application on heart rate

Of all mask applications preceded by spontaneous breathing, bradycardia was observed in 27% of applications and the HR decreased by >10 bpm in 19% of applications, with a maximum decrease of 79 bpm in one infant. Of the applications with a decrease in HR, the HR prior to mask application was >100 bpm in 92% of the applications and decreased <100 bpm in 25% of applications.

Bradycardia was overall significantly more often observed following the initial mask application compared with subsequent mask applications (initial: 61% and subsequent 21%, p<0.001).

The occurrence of bradycardia was most common in applications that also led to apnoea. In these cases, the risk of bradycardia was similar following the initial mask application and subsequent mask applications (initial: 73% and subsequent: 71%, p=0.607). However, in the cases where infants continued to breathe after mask placement, there was a significant difference in the occurrence of bradycardia following the initial mask application and subsequent mask applications (initial: 53% and subsequent: 5%, p<0.001) (table 3).

Table 2 Apnoea and bradycardia after mask application in infants with spontaneous breathing prior to application

	Initial application N=67	Subsequent application N=187	P value
Apnoea n (%)	32 (48)	44 (24)	<0.001*
Duration apnoea (s), median (IQR)	20.2 (9.4–31.2)	19.0 (9.5–46.2)	0.375†
Time until apnoea (s), median (IQR)	6.9 (2.0–16.3)	5.9 (0.43–14.9)	0.597†

*χ^2 test.
†Independent samples Mann-Whitney U test.

Effect of mask application on oxygen saturation

Of all mask applications preceded by spontaneous breathing, hypoxia was observed in 53% of applications and a decrease in SpO_2 of >10% was observed in only 8% of applications, with a maximum decrease of 22% in one infant.

Hypoxia was overall significantly more often observed following the initial mask application compared with subsequent mask applications (initial: 97% and subsequent: 44%, p<0.001).

Hypoxia following mask placement was often associated with apnoea. In these cases, there was no significant difference between initial mask application and subsequent mask applications (initial: 90% and subsequent: 86%, p=0.598). However, a significant difference in hypoxia between initial and subsequent mask application was observed in infants who continued to breathe after mask placement (initial: 100% vs subsequent: 31%, p<0.001) (table 3).

Effect of subsequent mask application on respiratory parameters

In infants who became apnoeic after subsequent mask applications, breathing rates were significantly reduced and minute volumes tended to decrease after mask application (breathing rate before 20.8 (14–32.4) vs after 16.0 (8.7–23.2) breaths/min, p<0.001; minute volume before 35.2 (13.6–84.1) vs after 24.4 (9.4–57.8) mL/min, p=0.064). However, in those infants who continued to breathe spontaneously after subsequent mask application, minute volumes were significantly increased (before 148.2 (96.2–202.9) vs after 157.6 (108.2–231.0) mL/min, p=0.041) after mask application (table 4).

Infants who became apnoeic after subsequent mask application had a significantly lower tidal volume, breathing rate and minute volume prior to the mask application compared with infants who continued breathing after mask application (table 4).

A logistic regression was performed to evaluate the effect of gestational age, duration of re-application, CPAP level, tidal volume, breathing rate, HR and SpO_2 prior to mask application on the likelihood that apnoea would occur after a subsequent mask application. The logistic regression model was statistically significant, χ^2 (7)=67.603, p<0.001. The model explained 70.3% (Nagelkerke R^2) of the variance in the occurrence of apnoea and correctly classified 93.9% of the cases. Lower breathing and HRs prior to mask application were associated with an increased likelihood of becoming apnoeic following subsequent mask applications (table 5).

DISCUSSION

This study has evaluated the effect of initial and subsequent mask applications on breathing and HR in preterm infants immediately after birth. Apnoea and bradycardia were commonly observed after mask placement, with apnoea and bradycardia occurring more often after initial compared with subsequent mask applications. This implies that repeated stimulation of the trigeminal nerve might lead to habituation and thus a diminished response during subsequent face mask application. In addition, low breathing and HRs prior to subsequent mask application were predictors for becoming apnoeic after subsequent mask application.

Table 3 Physiological parameters after initial and subsequent mask application in infants with spontaneous breathing prior to application

	All mask applications	Initial mask applications			Subsequent mask applications			Initial versus subsequent p values		
	Total N=254	Apnoea N=32	Breathing N=35	Total N=67	Apnoea N=44	Breathing N=143	Total N=187	Apnoea	Breathing	Total
Heart rate (bpm)	138 (110–155)	82 (63–110)	116 (89–1444)	104 (73–134)	102 (66–126)	149 (136–162)	142 (119–158)	0.509*	<0.001*	<0.001*
Bradycardia, n/n (%)	47/173 (27%)	8/11 (73)	9/17 (53)	17/28 (61%)	24/34 (71)	6/111 (5)	30/145 (21%)	0.607†	<0.001†	<0.001†
HR decrease >10 bpm, n/n (%)	26/135 (19%)	1/1 (100)	2/5 (40)	3/6 (50%)	8/26 (31)	15/103 (15)	23/129 (18%)	0.333†	0.175‡	0.085‡
SpO_2 (%)	86 (57–94)	57 (38–65)	53 (40–66)	55 (39–65)	57 (47–71)	92 (85–95)	89 (65–94)	0.662*	<0.001*	<0.001*
Hypoxia, n/n (%)	94/177 (53%)	9/10 (90)	20/20 (100)	29/30 (97%)	30/35 (86)	35/112 (31)	65/147 (44%)	0.598†	<0.001†	<0.001†
SpO_2 decrease >10%, n/n (%)	11/136 (8%)	0/1 (0)	2/5 (40)	2/6 (33%)	4/27 (15)	5/103 (5)	9/130 (7%)	0.857†	0.033‡	0.075‡
FiO_2 (%)	31 (29–46)	30 (28–30)	29 (28–30)	29 (28–30)	31 (29–60)	40 (30–48)	39 (29–49)	0.019*	<0.001*	<0.001*

*Independent samples Mann-Whitney U test.
†χ^2 test.
‡Fisher's exact test.
HR, heart rate; n/n, occurrence event/available measurements event.

Our results are consistent with our previous study reporting that in infants ≤32 weeks, approximately half stop breathing after initial mask placement.[2] We observed a similar percentage of infants who became apnoeic after initial mask placement even though our median gestational age was slightly lower (28+0 vs 28+6 weeks). As the occurrence of apnoea after initial mask placement is gestational age dependent,[2] a possible explanation for the similar percentages of apnoea could be that currently our caregivers are more aware of the possibility of inducing a TCR and apply the face mask more carefully.

The occurrence of habituation and a diminished response during subsequent mask application compared with initial application was also observed in a previous study evaluating the effect of initial and subsequent face mask applications on apnoea in term and late-preterm infants (>34 weeks). Gaertner *et al*[9] reported an incidence of apnoea in 29% of the initial applications compared with 8% of the subsequent applications. The large differences in the incidence of apnoea after initial and subsequent face mask application between this and our study can be explained by the differences in gestational age of the infants examined as the occurrence of TCR is gestational age dependent.[2] However, the incidence for a decrease in HR was similar in our study (19%) and that of Gaertner *et al*,[9] despite the differences in gestational age. It is possible that the effect of the TCR on HR was masked by other physiological factors that influence HR. For instance, many infants in our study were bradycardic, possibly caused by a loss in cardiac output as a result of umbilical cord clamping prior to establishing lung aeration and an increase pulmonary blood flow.[11] This might explain why a decrease in HR of >10 bpm was almost exclusively observed in infants with an HR >100 bpm prior to mask placement.

The occurrence of habituation and a diminished response to face mask application might be explained through three different mechanisms. The afferent cutaneous receptors of the TCR adapt rapidly to a continuous stimulus that is administered for a long duration with a relatively small rest interval. As a face mask is placed continuously for the duration of the stabilisation with only small rest intervals during mask repositions or re-applications, rapid sensory adaptation could assumably lead to habituation and a diminished response.[10] Second, the infant may have a higher end-expiratory lung volume after subsequent mask application, compared with the initial application, and as such is more resistant to hypoxia which likely contributes to the bradycardia. A larger end-expiratory lung volume would increase oxygen reserves within the lung, making the infant less susceptible to rapid desaturations in response to apnoea. Alternatively, it is possible that caregivers influence the infants' response to mask (re-)application by the amount of force they exert on the mask during neonatal stabilisation which might diminish over time.

As sensory adaptation seems to prevent the occurrence of apnoea after initial face mask application and in an animal study gradually increasing the continuous stimulus resulted in complete adaptation without firing of the afferent cutaneous receptors,[10] it might be possible that gradually increasing the exerted force by the caregiver during initial placement could lead to complete adaptation, and thereby preventing apnoea, if the exerted force by the caregiver is related to the occurrence of apnoea. Alternatively, use of an interface that provides sufficient pressure to the airways without activating the TCR may be more effective and warrants investigation.

This study is limited by its retrospective, observational design. The assessment of breathing via video recordings was dependent

Table 4 Respiratory parameters after subsequent mask application in infants with spontaneous breathing prior to subsequent mask application

	Subsequent mask application (n=187)						
	Apnoea following mask application N=44		P value*	Spontaneous breathing following mask application N=143		P value*	P value†
	Before	After		Before	After		
Tidal volume (mL/kg)	1.6 (0.6–4.4)	1.7 (0.8–3.8)	0.782	3.8 (2.7–5.2)	4.3 (3.0–5.6)	0.084	<0.001
Breathing rate (breaths/min)	20.8 (14.0–32.4)	16.0 (8.7–23.2)	<0.001	37.7 (29.0–49.9)	38.4 (32.5–46.3)	0.945	<0.001
Minute volume (mL/min)	35.2 (13.6–84.1)	24.4 (9.4–57.8)	0.064	148.2 (96.2–202.9)	157.6 (108.2–231.0)	0.041	<0.001

*Before versus after: Wilcoxon signed rank test.
†Before versus before: independent samples Mann-Whitney U test.

Table 5 Logistic regression analysis of infants with spontaneous breathing prior to subsequent mask application

		95% CI OR		
	OR	Lower	Upper	P value
Gestational age in weeks	1.424	0.778	2.608	0.252
Duration reposition	0.936	0.822	1.066	0.319
CPAP level (cm H_2O)	0.627	0.283	1.393	0.252
Tidal volume before application (mL/kg)	1.083	0.807	1.454	0.596
Breathing rate before application (breaths/min)	0.908	0.847	0.974	0.007
Heart rate (bpm)	0.935	0.901	0.970	<0.001
Oxygen saturation (%)	1.010	0.968	1.055	0.635

χ^2 (7)=67.603, p<0.05, R^2 (Nagelkerke): 0.703, correctly classified in 93.9% of the infants.
CPAP, continuous positive airway pressure.

on the visibility of the infant and the quality of the camera. In addition, the short timeframe to assess breathing during subsequent mask application made it often difficult to evaluate spontaneous breathing on camera during the application. However, assessing breathing before the initial mask placement and during subsequent application is only possible through retrospective video recordings or live assessment during the neonatal stabilisation. This makes it difficult to prove a causal relationship. Nevertheless, the ability to replay video recordings greatly increases the accuracy of the breathing assessment when measured visually.

CONCLUSION

Applying a face mask for non-invasive ventilation during neonatal stabilisation is associated with apnoea and bradycardia and this might be induced by the TCR. However, apnoea and bradycardia occurred more often after initial compared with subsequent mask applications in preterm infants, which may result from sensory adaptation of the trigeminal receptors. However, as infants with lower heart and breathing rates were at higher risk of apnoea following mask re-application, this reflex is clearly modified by other factors. Clinicians should be careful in applying a face mask for non-invasive support at birth as it might compromise the breathing that they intend to support.

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Contributors KLAMK: co-conceived the study, conducted the study, collected, analysed and interpreted the data, wrote the first draft of the manuscript and approved the final version of the manuscript. AH: conducted the study, collected and interpreted the data, reviewed and edited the manuscript and approved the final version of the manuscript. SJEC, JD, RV, SBH: data interpretation, reviewed and edited the manuscript and approved the final version of the manuscript. ABtP: guarantor, co-conceived the study, supervised the study, interpreted the data, reviewed and edited the first draft of the manuscript and approved the final version. All authors agree to be accountable for all aspects of the work.

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Patient consent for publication Not applicable.

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