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Heart Rate Changes following Facemask Placement in Infants Born at ≥32^{+0} Weeks of Gestation

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Keywords
Neonate · Resuscitation · Heart rate · Bradycardia · Ventilation · Trigeminocardiac reflex

Abstract
Introduction: Recent reports have raised concerns of cardiorespiratory deterioration in some infants receiving respiratory support at birth. We aimed to independently determine whether respiratory support with a facemask is associated with a decrease in heart rate (HR) in some late-preterm and term infants. ***Methods:*** Secondary analysis of data from infants born at ≥32^{+0} weeks of gestation at 2 perinatal centres in Melbourne, Australia. Change in HR up to 120 s after facemask placement, measured using 3-lead electrocardiography, was assessed every 3 s until 60 s and every 5 s thereafter from video recordings. ***Results:*** In the 15 s after facemask placement, 10/68 (15%) infants had a decrease in mean HR by >10 beats per minute (bpm) compared with their individual baseline mean HR in the 15 s before facemask placement. In 4 (6%) infants, HR decreased to <100 bpm. Nine out of 68 (13%) infants had an increase in mean HR by >10 bpm; 7 of these infants had a baseline HR <120 bpm. In univariable comparisons, the following characteristics were found not to be risk factors for a decrease in HR by >10 bpm: prematurity; type of respiratory support; hypoxaemia; early cord clamping; mode of birth; HR <120 bpm before mask placement. Six out of 63 infants (10%) who had HR ≥120 bpm after facemask placement had a late decrease in HR to <100 bpm between 30 and 120 s after facemask placement. ***Conclusion:*** Facemask respiratory support at birth is temporally associated with a decrease in HR in a subset of late-preterm and term infants.

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Introduction

Respiratory support delivered via a facemask remains the mainstay of newborn stabilisation [1]. Recent studies have found that some infants show signs of clinical deterioration

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upon the initiation of respiratory support using a facemask [2, 3]. These studies describe apnoea and bradycardia that are most pronounced in preterm infants following the first instance of facemask placement [4].

It is suggested that placement of a facemask triggers the trigeminocardiac reflex (TCR) by stimulating the trigeminal nerve [2]. The TCR is a brainstem reflex that includes the diving reflex and is activated by application of stimuli to the face. Afferent signals from the trigeminal nerve activate brainstem pathways that signal via parasympathetic vagal neurons to induce rapid cardiorespiratory changes including apnoea and decreases in both heart rate (HR) and blood pressure [5, 6]. The role of physiological factors, such as degree of asphyxia, on modulating the TCR is not well known.

HR is regarded as the most important marker of infant well-being after birth [1, 7, 8] and is a major determinant of cardiac output [9]. While a low HR can indicate hypoxia, other factors that modify HR include vagally mediated parasympathetic activation (including the TCR), sympathetic activation from peri-partum hypoxic-ischaemia, and alterations in cardiac preload [10]. Newborn resuscitation algorithms recommend maintaining HR >100–120 beats per minute (bpm) [1].

We aimed to independently validate the observations of others [3, 4] by determining whether the initiation of respiratory support with a facemask in late-preterm and term infants is temporally associated with a decrease in HR. We additionally aimed to describe the timeframe over which the decrease in HR occurs and define characteristics to identify infants most at risk.

Methods

We used data from infants concurrently recruited to a randomised controlled trial and prospective cohort study at the Royal Women's Hospital (RWH) and Monash Medical Centre (MMC) in Melbourne, Australia [11, 12]. Approval was obtained from each site's Human Research Ethics Committee. Written informed consent was obtained from the parents for participation in the study, and deferred consent was used at the RWH site in emergency situations where prospective consent was not possible. Participants for this study were recruited between August 5, 2018, and April 2, 2020. There was no pre-specified sample size for this secondary analysis.

Participants

Infants were eligible for participation in the primary study if they fulfilled the following inclusion criteria [11]:

- $\geq 32^{+0}$ weeks of gestation at birth
- Paediatric doctor requested to attend an at-risk birth
- Researcher present at the birth

Infants with any of the following criteria were excluded:

- Known congenital anomalies compromising cardiorespiratory transition
- High risk of obstetric complications requiring early cord clamping
- Monochorionic twins

Infants assessed as requiring resuscitation within 1 min of birth were randomised to either physiologically based cord clamping, where resuscitation was commenced and respiratory support, if needed, could be provided prior to umbilical cord clamping, or standard care, where cord clamping occurred early prior to resuscitation. Infants who were vigorous immediately after birth were not randomised and instead were included in the observational cohort study. These infants had cord clamping deferred for >2 min. Some non-randomised infants went on to receive respiratory support in the delivery room. Infants in both the randomised and non-randomised study arms were included in the present analysis if they received facemask respiratory support. Respiratory support was provided with facemask (Laerdal or Fisher & Paykel) and T-piece connected to a Giraffe Stand-alone resuscitation system (GE Healthcare, USA) set to pressures of 30/5 cm H_2O in 21% FiO_2. The type and decision to initiate respiratory support were at the discretion of the first-line clinician trained in the Australian and New Zealand Committee on Resuscitation Neonatal Resuscitation Guidelines [13]. We did not ask for the clinician's specific reasoning and therefore did not collect data on indications for respiratory support.

Data Acquisition

Immediately after birth, a researcher dried the infant and placed 3 ECG chest leads and a preductal pulse oximeter to monitor the infant's HR and oxygen saturation (SpO_2). These were displayed on a portable IntelliVue X2 (Philips Healthcare, USA) or Infinity M540 (Dräger, Germany) monitor. A GoPro Hero Session (GoPro, USA) captured the monitor screen, T-piece manometer, oxygen blender dial and an audio recording of the events after birth. The videos were downloaded for offline data extraction.

Data were manually extracted offline from the video recordings to ensure high fidelity. HR was documented every 3 s from 15 s prior to mask placement until 30 s after mask placement, and every 5 s thereafter until 120 s after mask placement. If the monitor did not display a HR number, or if the HR was rapidly changing, the HR was calculated by measuring the distance (in screen pixels) between adjacent QRS complexes (minimum 3 complexes) as a ratio of the length (in screen pixels) of the monitor screen. The monitor screen had a known time duration of 3 or 4 s (IntelliVue X2 or Infinity M540, respectively). The time of initiation of respiratory support was determined by the increase in pressure seen on the T-piece manometer upon facemask placement. Baseline SpO_2 for each infant was determined by calculating the mean of SpO_2 readings obtained every 3 s in the 15 s before facemask placement. All data points following suction of the oropharynx were excluded.

Study Outcomes

Baseline HR for each infant was determined by calculating the mean of HR readings obtained every 3 s in the 15 s before facemask placement. The primary outcome was pre-specified as the proportion of infants who had a decrease in mean HR by >10 bpm in the 15 s following mask placement compared with their individual baseline HR. Both the threshold (>10 bpm) and timeframe were based on the findings of previous studies [3, 4]. A time point close to the placement of the facemask was felt to more reliably represent a temporal association between exposure and outcome by limiting interference from external, uncontrolled factors [14]. To assess whether an infant's HR was already on a downward trend, we evaluated HR stability during the baseline period. The HR was considered stable if the range of HR values during the 15 s before facemask placement was within +/– 10% around the mean baseline HR. Only the first application of the facemask with adequate HR data was evaluated.

We pre-specified the following secondary outcomes:

1. The proportion of infants who had a decrease in mean HR by >10 bpm in the 30 s and 60 s after facemask placement compared with their individual baseline mean HR in the 15 s before facemask placement.
2. The proportion of infants with a late decrease in HR – those infants with HR >120 bpm at any point within 30 s of facemask placement, for whom HR subsequently dropped to <100 bpm at any time point between 30 and 120 s after facemask placement. If the facemask was taken off during this timeframe, the subsequent HR data were excluded.

We additionally report as a post hoc secondary outcome the proportion of infants with an increase in HR by > 10 bpm in the 15 s after facemask placement compared to their mean HR in the 15 s before facemask placement.

Subgroup Analysis

We evaluated the following pre-specified variables based on previous studies and clinical experience that might modify the effect of facemask placement on decrease in HR [2, 3, 15]:

1. Gestational age: $<37^{+0}$ weeks versus $\geq 37^{+0}$ weeks;
2. Positive pressure ventilation (PPV) versus continuous positive airway pressure (CPAP) at the time of facemask placement;
3. Mean SpO_2 <10th centile (based on the percentiles published by Dawson et al. [16] from infants who had immediate cord clamping) versus mean SpO_2 ≥10th centile in the 15 s before facemask placement;
4. Deferred versus early cord clamping;
5. Vaginal versus caesarean birth;
6. Mean HR: ≥120 bpm versus <120 bpm in the 15 s before facemask placement.

Data Analysis

Data from infants who received respiratory support were analysed if they met the following pre-specified data requirements:

- For the pre-post facemask placement analysis, infants were included if they had >50% of the HR data points in both the 15 s before and any of the 15, 30, or 60 s after facemask placement.
- For the late decrease in HR analysis, infants were included if their highest HR was ≥120 bpm in the 30 s after facemask placement and at least one HR data point in the 30–120 s after facemask placement was available.

Individual participant HR changes after facemask placement are shown in scatterplots. The number of infants who had a decrease in HR is presented as a proportion of infants with available data. Comparisons of proportions of infants in the subgroup analyses were performed using a Fisher's exact test. Analyses were performed with SPSS Statistics 25.

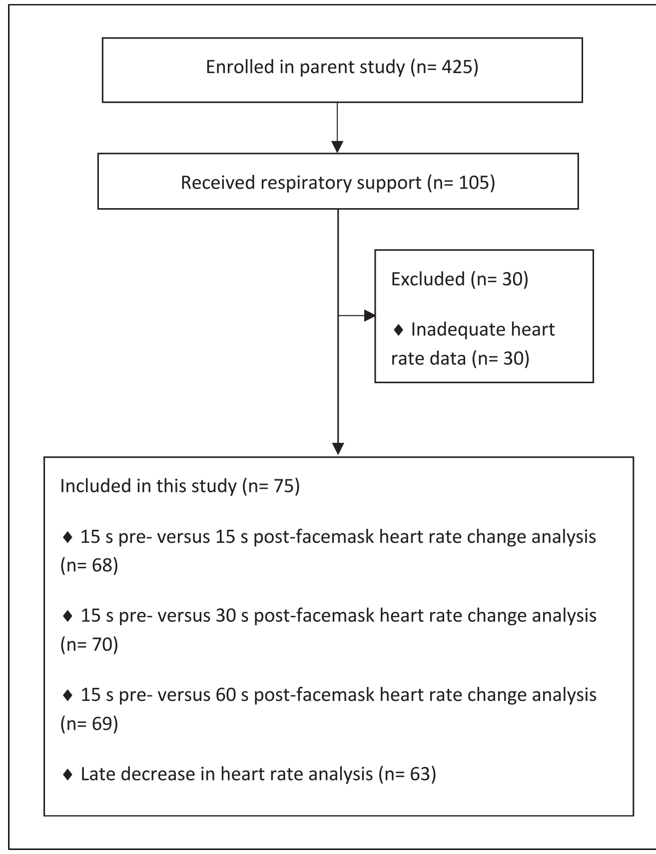

Fig. 1. Flow diagram of study participants. For the pre-post facemask placement analysis, infants were included if they had >50% of the HR data points (obtained every 3 s) in both the 15 s before and any of the 15, 30, or 60 s after facemask placement.

Results

Respiratory support was provided to 105 infants in the first 10 min after birth. Thirty infants were excluded due to inadequate HR data (Fig. 1). Baseline characteristics are shown in Table 1. The median (IQR) gestational age was 39^{+1} (37^{+6}–40^{+2}) weeks.

Of the 75 included infants, adequate data were available for 62 infants with instances of the first facemask application and 13 infants with a subsequent facemask application. Thirty-two infants were in the randomised trial having been assessed as requiring resuscitation within 1 min of birth; 11 of these infants received PPV and 20 received CPAP. Among 45 non-randomised infants, 6 received PPV and 38 received CPAP. Infants receiving PPV had respiratory support commenced at a median (IQR) of 63 (41–112) s, likely indicating concerns regarding apnoea and/or

Table 1. Participant characteristics

	All infants, (N = 75)
Antenatal	
Primiparous, *n* (%)	62 (83)
Maternal analgesia, *n* (%)	
None or nitrous oxide	4 (5)
Opiate	2 (3)
Spinal or epidural	67 (89)
General anaesthetic	2 (3)
Foetal compromise, *n* (%)	
None	27 (36)
Meconium	21 (28)
Abnormal CTG	39 (52)
Reduced foetal movements	5 (7)
Abnormal Doppler	4 (5)
Mode of birth, *n* (%)	
Unassisted vaginal	2 (3)
Instrumental vaginal	17 (23)
Planned CS	13 (17)
Unplanned CS	43 (57)
Antenatal corticosteroids, *n* (%)	13 (17)
Neonatal	
Gestational age in weeks, median (IQR)	39^{+1} (37^{+6}–40^{+2})
Birth Weight in g, median (IQR)	3,290 (2,890–3,796)
Cord clamped >60 s, *n* (%)	57 (76)
Males, *n* (%)	35 (47)
Arterial cord pH, median (IQR)	7.20 (7.11–7.26)[a]
Arterial cord lactate, median (IQR)	4.4 (3.3–5.9)[b]
SpO_2 at time of facemask placement <10th centile, *n* (%)	32/52 (62)[c]
Time after birth when the facemask was placed in s, median (IQR)	177 (91–230)
CPAP as initial respiratory support, *n* (%)	58 (77)
Unstable HR during the 15 s before mask placement*, *n* (%)	9/70 (13)[d]

CPAP, continuous positive airway pressure; CTG, cardiotocogram; CS, caesarean section; IQR, interquartile range. [a]44 (59%) with available data. [b]45 (60%) with available data. [c]52 (69%) with available data. [d]70 (93%) with available data. *HR was considered stable if the range of baseline HR values during the 15 s before facemask placement was +/− 10% around the mean baseline HR.

bradycardia shortly after birth. Due to the typical time taken to establish an SpO_2 reading, only 3/17 infants had SpO_2 data prior to commencing respiratory support. SpO_2 was <10th centile for in all 3 infants. In contrast, infants receiving CPAP commenced respiratory support later, at a median (IQR) of 192 (129–244) s after birth. CPAP was typically commenced for signs of respiratory distress and/or hypoxaemia (29/58 infants had SpO_2 <10th centile, 9 had no SpO_2 data available). All infants commenced CPAP with FiO_2 of 0.21 and pressure of 5 cm H_2O, as per local guidelines.

Within 15 s of facemask placement, 10/68 (15%) infants had a decrease in mean HR by >10 bpm compared with their individual baseline mean HR in the 15 s before facemask placement. In 6/68 (9%) infants, the HR reduced to <120 bpm and, in 4/68 (6%), to <100 bpm. Two of these infants had an unstable baseline HR (as defined above); one infant had a consistently falling HR, and the other had a HR that both increased and decreased (Fig. 2, Table 2). In contrast, 9/68 (13%) infants had an increase in mean HR by >10 bpm. Among infants with a low baseline HR (<120 bpm), 7/15 (47%) demonstrated an increase in mean HR by >10 bpm; 5 of these infants had an unstable baseline HR (Fig. 2).

Compared with their individual baseline mean HR in the 15 s before facemask placement, the mean HR decreased by >10 bpm within 30 s and 60 s after facemask placement in 17/70 (24%) and 15/69 infants (22%), respectively (Fig. 2; Table 2). In total, 20/75 (27%) infants had a decrease in HR of 15, 30, or 60 s after facemask placement. The difference between

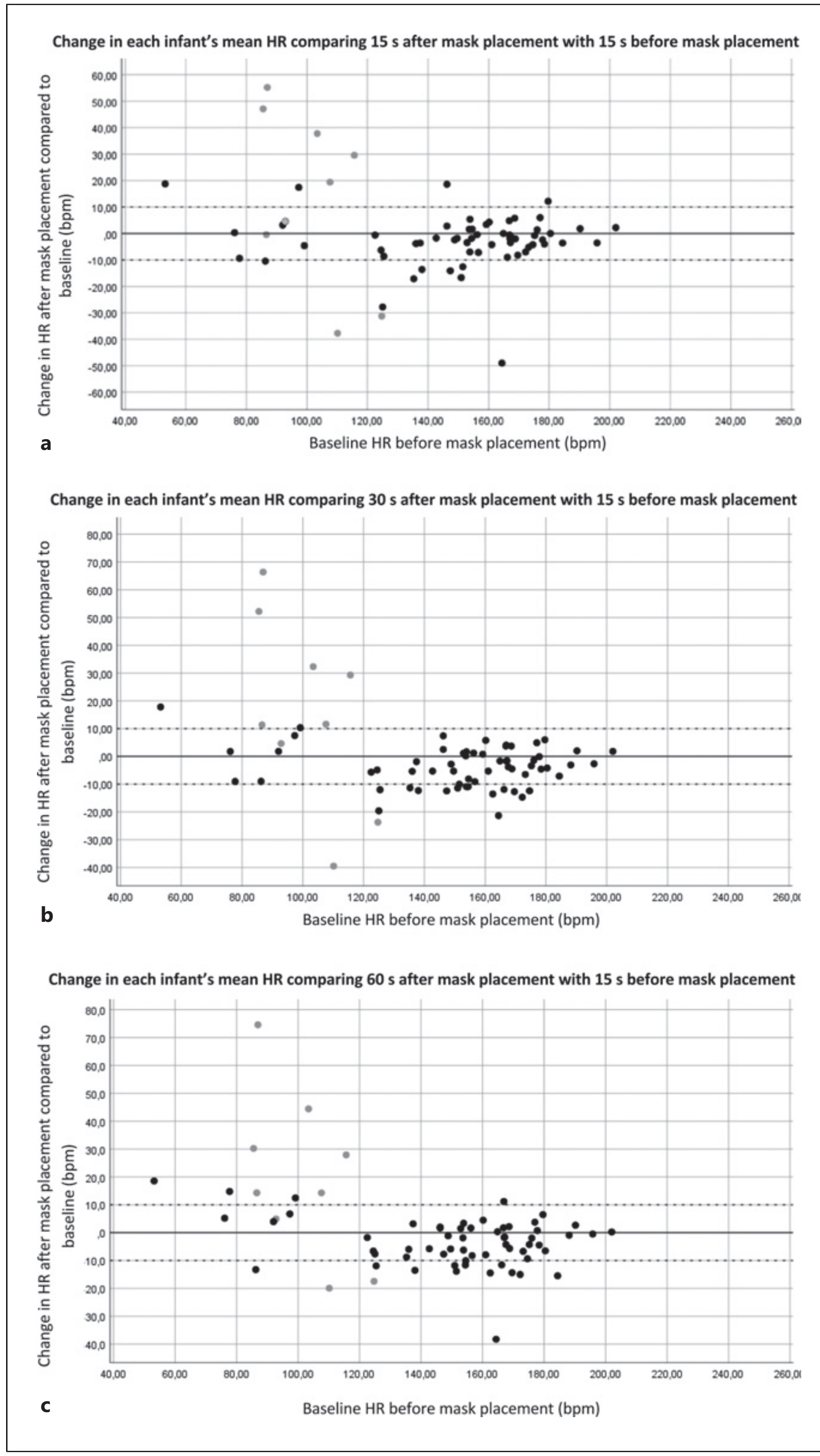

Fig. 2. Individual infant HR change 15 s after mask placement (**a**), 30 s after mask placement (**b**), and 60 s after mask placement (**c**), in relation to the individual baseline mean HR over the 15 s before mask placement. Grey dots represent infants with an unstable baseline HR, where the HR may have been rising, falling, or fluctuating prior to facemask placement. HR was considered stable if the range of baseline HR values during the 15 s before facemask placement was within +/− 10% around the mean HR during that period.

Table 2. Heart rate (HR) changes for the entire cohort after mask placement

	Infants with a decrease in HR by >10 bpm, *n* (%)	Infants with a decrease in HR by >10 bpm to <120 bpm, *n* (%)	Infants with a decrease in HR by >10 bpm to <100 bpm, *n* (%)
15 s post mask placement*	10/68 (15)	6/68 (9)	4/68 (6)
30 s post mask placement*	17/70 (24)	6/70 (9)	3/70 (4)
60 s post mask placement*	15/69 (22)	5/68 (7)	3/68 (3)

bpm, beats per minute; HR, heart rate. *For each time point, 2 infants had an unstable baseline HR prior to facemask placement; one infant had a consistently falling HR, and the other had a HR that rose and fell.

the individual baseline HR and the lowest observed HR value for each of these 20 infants ranged between 20 bpm and 109 bpm, with a median (interquartile range) of 32 (26–40) bpm.

In the univariable subgroup analyses, we found no evidence of a difference in the proportion of infants with and without pre-specified characteristics who had a decrease in HR after facemask placement (Table 3). Six out of 63 infants (10%) had a late decrease in HR to <100 bpm between 30 and 120 s after facemask placement, after their HR had been >120 bpm in the 30 s after facemask placement.

Discussion

We found that facemask respiratory support is temporally associated with a clinically important decrease in HR in a subset of infants born at $\geq 32^{+0}$ weeks of gestation. The decrease in HR occurs rapidly (within 15 s), but in some cases, it occurred up to 120 s after the initiation of respiratory support. This study highlights the high degree of variation between individuals in response to facemask application, which likely indicates that the underpinning physiology is multifactorial and may depend on the physiological state of the infant when the facemask is applied.

The intention of respiratory support is to assist transition. Our data indicate that the HR range upon commencement of respiratory support is wide. Most infants with low or unstable baseline HR had a substantial rise in HR that could have resulted from improved lung aeration and increased cardiac preload [17]. However, as the response occurred within 15 s, this is unlikely. Instead, it is possible that these infants were initially more "depressed" physiologically, suppressing the TCR. Depressed infants are usually asphyxic, and asphyxia, depending on the severity, is well known to suppress most reflexes [18]. For instance, as newborns progressively become asphyxic, one of the first responses is to lose arousal and muscle tone. As this is controlled by sensory feedback from a variety of receptors, including joint receptors, muscle spindles, and proprioreceptors, input from these receptors must be overridden by higher centres to suppress their feedback response. Suppression of many of these reflexes has been described in detail, even down to the higher brain centres that are activated [19]. While there are no studies demonstrating the inhibitory effect of asphyxia on the TCR, in our opinion, it would be very unusual if asphyxia did not have a similar inhibitory effect on this reflex. With the TCR suppressed, facemask application may have provided physical stimulation that increased arousal, leading to the rise in HR observed.

In contrast, infants who had a clinically relevant decrease in HR in the 15–60 s after facemask placement typically had a higher baseline HR. These infants were arguably in a better physiological state (higher HR) prior to facemask placement, with less inhibition of foetal reflexes, triggering a predictable TCR response. Notably, 10% of infants had a late decrease in HR to <100 bpm between 30 and 120 s after facemask placement, but the physiology underpinning this delay is hard to explain. We did not find a difference in risk among various subgroups; however, the small numbers of infants in the subgroups may be insufficient to make meaningful comparisons.

Our findings are consistent with a recent study by Gaertner et al. [3]. They reported in infants born at >34 weeks of gestation that HR decreased by ≥10 bpm in 10 of 51 (20%) facemask applications with adequate data, and 2 applications (4%) were followed by a bradycardia of <100 bpm. These proportions are similar to our observations.

We did not take video recordings of the infants and were unable to assess the effectiveness of respiratory support. It is possible that placement of the facemask resulted in airway obstruction or excessive leakage, resulting in progressive hypoxia [20]. However, this

Table 3. Univariable comparisons of the proportion of infants in each subgroup who had a decrease in HR >10 bpm

Subgroup	Infants with a decrease in HR >10 bpm 15 s after mask placement, *n* (%)	*p* value	Infants with a decrease in HR >10 bpm 30 s after mask placement, *n* (%)*	*p* value
Mean HR 15 s pre-mask placement				
≥120 bpm	8/53 (15)	1.00	16/55 (29)	0.10
<120 bpm	2/15 (13)		1/15 (7)	
Respiratory support				
CPAP	7/55 (13)	0.39	12/55 (22)	0.50
PPV	3/13 (23)		5/15 (33)	
SpO_2 at the point of mask placement				
≥10th centile	4/20 (20)	0.41	8/20 (40)	0.12
<10th centile	3/32 (9)		6/32 (19)	
Cord clamping				
>60 s after birth	6/54 (11)	0.20	12/55 (22)	0.50
<60 s after birth	4/14 (29)		5/15 (33)	
Gestational age				
$\geq 37^{+0}$ weeks	6/53 (11)	0.21	11/55 (20)	0.17
$<37^{+0}$ weeks†	4/15 (27)		6/15 (40)	
Vaginal birth	1/14 (7)	0.67	2/16 (13)	0.32
Caesarean birth	9/54 (17)		15/54 (28)	

p value from Fisher's exact test. Bpm, beats per minute; CPAP, continuous positive airway pressure; HR, heart rate; PPV, positive pressure ventilation; SpO_2, oxygen saturation. *Post hoc analysis performed as there was a greater *n* of infants with a decrease in HR 30 s after facemask placement. †Preterm infants had median (IQR) gestational age of 34 (33^{+1}–35^{+3}) weeks.

would be expected to take longer than 15 s to decrease HR. Previous studies have suggested that the TCR is likely to play a role [2, 3]. Apnoea is a primary component of TCR activation and has been reported in 50% of very preterm infants following the first facemask application after birth [4]. It is possible that TCR-induced apnoea is less common in late-preterm and term infants than in very/extremely preterm infants, possibly due to a higher state of arousal immediately after birth that overrides TCR activation. Both the frequency and clinical implications of HR reduction following facemask placement are likely to be greater in very/extremely preterm infants.

A strength of this study was that we used ECG, which is less susceptible to signal interference than pulse oximetry [1, 21]. As a result, we obtained HR data from 70% of infants who received respiratory support in comparison to 40% in the study by Gaertner et al. [3].

This study has important limitations. It is possible that the change in HR, measured repeatedly, represents a random distribution at each time point. When measuring HR before and after facemask placement, the phenomenon of "regression to the mean" can result in infants with a relatively high HR appearing to have a reduction in HR and vice versa [22]. We mitigated this issue by using a threshold of 10 bpm to filter noise from natural variation in the repeated HR measurements. Additionally, we mitigated the issue of regression to the mean by evaluating the change in HR for all infants, not just those at the extremes of HR before facemask placement [23]. We did not have a control group of infants who did not receive facemask ventilation. To ascertain whether the HR was already decreasing, we evaluated HR stability during the 15 s before facemask placement; most infants had a stable baseline HR. We restricted the primary analysis to the 15 s timeframe to limit the possibility of interference from other uncontrolled or changing physiological factors. Of the 75 included infants, 13 infants only had adequate HR data with a subsequent facemask application – as the TCR is typically more prominent upon the first facemask application, the risk of HR decrease may be underestimated.

Further work to evaluate strategies that mitigate bradycardia after initiation of respiratory support is warranted. This is particularly relevant for the more stable infants with baseline HR >120 bpm, where commencement of respiratory support is less urgent. When respiratory support is provided, it is possible that more careful downward pressure on the facemask, use of humidified gases, concurrent stimulation, or alternative devices such as bi-nasal prongs may have a protective effect [10, 24, 25]. At present, our findings and those of others would justify recommendations to be vigilant for unexpected early decreases in HR following facemask placement.

Statement of Ethics

All study procedures were approved by the Human Research Ethics Committees at the Royal Women's Hospital (reference number 17/19) and Monash Health (reference number RES-18-0000-035A). Written informed consent was obtained from the parents for participation in the study. Deferred parental consent was used at the Royal Women's Hospital site if the participant became eligible only immediately prior to an emergency birth when prospective consent could not be sought, as approved by the Human Research Ethics Committees at the Royal Women's Hospital.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Study conceptualization and methodology: S.B. and P.D.; approvals and recruitment: S.B., D.B., P.D., and C.R.; data curation and analysis: E.B., S.B., and K.K.; interpretation and supervision: E.B., S.B., K.K., At.P., G.P., S.H., and P.D.; writing – original draft: E.B. and S.B.; and writing – reviewing and editing: all authors.

Data Availability Statement

The data that support the findings of this study will be made openly available from the Monash University Research Repository upon acceptance of the manuscript for publication. Further enquiries can be directed to the corresponding author.

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