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Clinical paper

A multi-centre randomised controlled trial of respiratory function monitoring during stabilisation of very preterm infants at birth

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Abstract

Aim: To determine whether the use of a respiratory function monitor (RFM) during PPV of extremely preterm infants at birth, compared with no RFM, leads to an increase in percentage of inflations with an expiratory tidal volume (Vte) within a predefined target range.

Methods: Unmasked, randomised clinical trial conducted October 2013 - May 2019 in 7 neonatal intensive care units in 6 countries. Very preterm infants (24–27 weeks of gestation) receiving PPV at birth were randomised to have a RFM screen visible or not. The primary outcome was the median proportion of inflations during manual PPV (face mask or intubated) within the target range (Vte 4–8 mL/kg). There were 42 other prespecified monitor measurements and clinical outcomes.

Results: Among 288 infants randomised (median (IQR) gestational age 26^{+2} (25^{+3}–27^{+1}) weeks), a total number of 51,352 inflations were analysed. The median (IQR) percentage of inflations within the target range in the RFM visible group was 30.0 (18.0–42.2)% vs 30.2 (14.8–43.1)% in the RFM non-visible group (p = 0.721). There were no dierences in other respiratory function measurements, oxygen saturation, heart rate or FiO_2. There were no dierences in clinical outcomes, except for the incidence of intraventricular haemorrhage (all grades) and/or cystic periventricular leukomalacia (visible RFM: 26.7% vs non-visible RFM: 39.0%; RR 0.71 (0.68–0.97); p = 0.028).

Conclusion: In very preterm infants receiving PPV at birth, the use of a RFM, compared to no RFM as guidance for tidal volume delivery, did not increase the percentage of inflations in a predefined target range.

Trial registration: Dutch Trial Register NTR4104, clinicaltrials.gov NCT03256578.

Keywords: Neonatal resuscitation, Preterm infants, Respiration, Monitoring, Tidal volume

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Introduction

Preterm infants often fail to breathe and establish effective gas exchange at birth. Therefore, most infants receive mask ventilation or are intubated in the delivery room (DR).[1,2] The combined need for respiratory support during the physiological transition at birth and the narrow therapeutic target range for expired tidal volume (Vte) make the first minutes of life a vulnerable time. Positive pressure ventilation (PPV) can be a necessary form of respiratory support, but may injure the lungs through shear stress or high tidal volumes. These injuries can cause hemodynamic instability, and trigger a systemic inflammatory cascade, possibly leading to cerebral injury.[3] Therefore, improving respiratory support of extremely preterm infants at birth may improve long-term outcomes.

International resuscitation guidelines recommend assessing heart rate (HR) and oxygen saturation (SpO_2).[4] However, measurements for reliable assessment of spontaneous breathing and provision of respiratory support are lacking.[4] Guidelines suggest the use of set inflating pressures and monitoring chest excursions to guide ventilation. However, observing chest excursion to estimate Vte is unreliable.[5,6] Caregivers set peak inspiratory pressure (PIP) and positive end-expiratory pressure (PEEP) during resuscitation but these do not accurately reflect the delivered tidal volume.[7]

To avoid lung injury, non-invasive respiratory support (e.g. continuous positive airway pressure (CPAP), PPV) is now recommended for extremely preterm infants at birth. However, these modes of support are often hampered by variable mask leak and airway obstruction, which contribute to inadequate Vte delivery.

Manikin and clinical studies[8] have shown the use of a respiratory function monitor (RFM) measuring and displaying ventilation pressures, gas flow, inspired and expired tidal volume (Vti, Vte), mask leak, heart rate (HR), peripheral oxygen saturation (SpO_2) and inspired oxygen (FiO_2) can guide the application of PPV in the delivery room (DR). Using a RFM enables the caregiver to quickly recognise mask leak, airway obstruction and inadequate or excessive Vte.[8] Although it seems logical to use a RFM when providing PPV, having an extra monitor could distract the caregiver from ventilation, particularly when inexperienced with using an RFM. Small RCTs reported a beneficial effect with less high Vte and mask leak when an RFM was present, but data from larger trials remain lacking.[9,10] Therefore, the aim of this study was to determine whether using a RFM during PPV in preterm infants in the DR leads to delivery of a greater percentage of inflations in a predefined Vte range.

Methods

Study design

The Monitoring Neonatal Resuscitation (MoNitoR) trial (Dutch Trial Register NTR4104, clinicaltrials.gov NCT03256578) was a pragmatic, unblinded, randomised trial in 7 Neonatal Intensive Care Units (NICUs) in 6 countries (Netherlands, Australia, Germany, Spain, Italy, United States; October 2013-May 2019). The Institutional review boards (IRBs) at each centre approved the study. Informed consent was obtained from parents of all participants included in the analyses. At 5/7 sites, deferred consent was endorsed when there was insufficient time for antenatal consent, or considered inappropriate.

Participants

Infants between 24^{+0} weeks and 27^{+6} weeks of gestation were included if they received PPV at birth. Infants were excluded if they had a congenital anomaly that might affect breathing or ventilation.

Randomisation

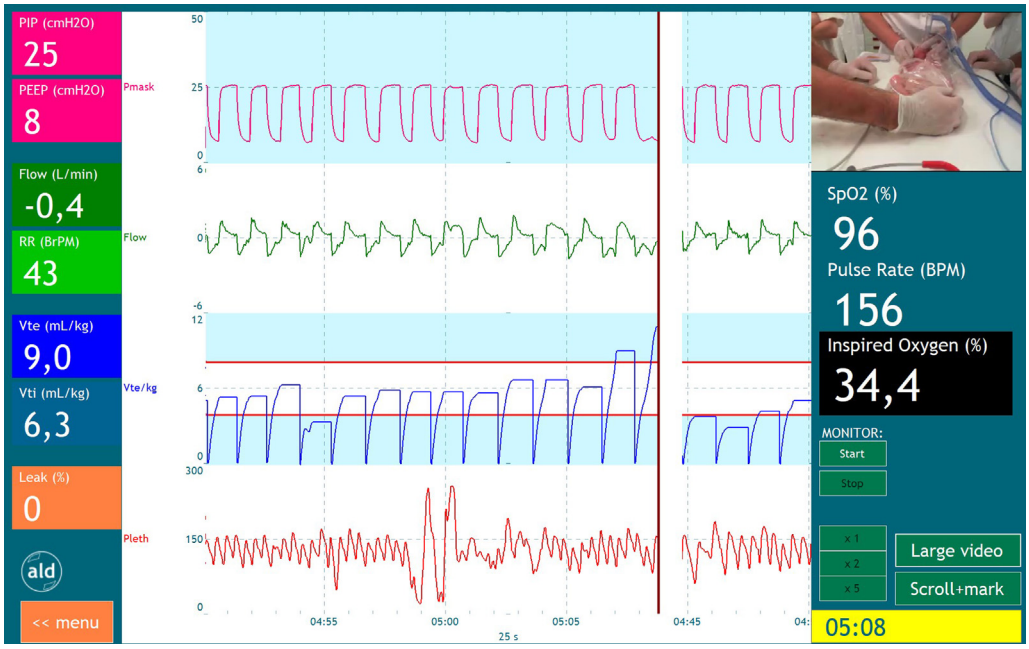
Infants were randomised to either a visible or non-visible RFM. Randomisation was performed using computer allocation, stratified by centre and gestational age (24–25 and 26–27 weeks) using variable block (4–8) sizes. Concealment of randomisation before birth was achieved using opaque, gestational age-stratified sealed envelopes that were kept in the delivery wards. In case of multiple births: if two RFMs were available each infant was randomised separately. If only one RFM was available, and there was no time to use it for the second infant, only the first baby was included. The envelope was opened shortly before each infant's birth by one of the caregivers present at birth. Due to the nature of the intervention, blinding was not possible. The analysis of RFM data was performed at the Leiden University Medical Centre (LUMC) by investigators blinded to the allocation.

Intervention

All personnel involved in the trial were trained in the use of the RFM before trial commencement. The training took place at each participating centre at the discretion of local experts. All other resuscitative measures followed local protocols. All centres used a T-piece (Neopuff™ Fisher&Paykel®) with a gas flow rate of 8 L/min and face mask when providing PPV to an infant. If necessary, infants were intubated and included in the analysis if the intubation was completed within the first ten minutes of respiratory support.

The RFM was the ALD resuscitation monitor (Advanced Life Diagnostics, Weener, Germany). This monitor contained Polybench software (Advanced Life Diagnostics, Weener, Germany) which digitised and recorded at 200 Hz all signals from the New Life Box (NLB) physiological recording system (Advanced Life Diagnostics, Weener, Germany). The NLB utilises a dead space (1 mL) variable orifice anemometer (AveaVarflex Flow Transducer, Carefusion, Yorba Linda, CA, USA) to measure circuit pressure and gas flow in and out of a T-piece. The signal was automatically integrated to provide Vti and Vte and calculate mask leak. SpO_2 and HR were measured with a Masimo SET pulse-oximeter (Masimo Radical, Masimo Corporation, Irvine, California, USA) or a Philips Intellivue MP30 Patient Monitor (Philips, Amsterdam, Netherlands) with a probe around the right hand. FiO_2 was measured with an oxygen analyser AX300-I (Teledyne Analytical Instruments, City of industry, CA, USA) in the tubing leaving the Neopuff™. A video of each resuscitation was recorded (Picture 1).

The following parameters were displayed on the RFM (Picture 1): PIP, PEEP, respiratory rate, Vti, Vte, mask leak, HR, SpO_2, FiO_2 and a timer. The pressure, flow and Vte (mL/kg) waves were displayed. The Vte target range limits (4–8 mL/kg) were shown as two red lines.[11] Caregivers were instructed to aim for a Vte in this range.



Picture 1 – Respiratory Function Monitor Display. Numeric data displayed on the left side of the screen include peak inspiratory pressure (PIP, cm H_2O), positive end-expiratory pressure (PEEP, cm H_2O), flow (L/min), respiratory rate (inflations per minute), expired and inspired tidal volume (Vte (mL/kg), Vti (mL/kg)), and mask leak (%) for the time at the vertical red line. Waveform data displayed in the middle of the screen include pressure (cm H_2O), flow (mL/min), expired tidal volume (mL/kg) and the plethysmograph of the pulse-oximeter. The red horizontal lines in the Vte waveform delineate the target range of 4–8 mL/kg. The right side of the screen includes the camera view, oxygen saturation (SpO_2, %), heart rate (pulse rate, bpm), fraction of inspired oxygen (FiO_2, %) and the time (min:sec) from birth. The data displayed on the screen represent real-time values of each respiratory parameter at the vertical red line.

It was possible to enter the estimated birth weight and/or gestational age before mask ventilation or switch to the measured birth weight at birth.

When the infant was randomised to the visible group, the screen was visible and started recording at time of birth. When the infant was randomised to the non-visible group, the screen was black, but the monitor started recording at time of birth for data analysis.

Primary outcome

The primary outcome was the percentage of inflations during manual PPV (face mask or intubated) within the target range (Vte 4–8 mL/kg) within the first 10 minutes of respiratory support.

Secondary outcomes

Secondary RFM outcome parameters included average SpO_2, HR and FiO_2 during the first 10 minutes from birth, duration of mask leak > 60 % as a percentage of time of mask ventilation, airway obstruction (defined as Vte < 1 mL/kg, with minimal mask leak (<25%) during an inflation and flattening of the flow waves). Recordings were reviewed and mask adjustments, pressure adjustments and suctioning during the first 10 minutes were documented.

Clinical secondary outcomes included endotracheal intubation within 24 h after birth, inotropes or fluid boluses within 24 h, pneumothorax or pulmonary interstitial emphysema in the first 72 hours, cerebral injury defined as abnormal cranial ultrasound findings: (i) all intraventricular haemorrhage (IVH), (ii) severe IVH (i.e. Papile grade III and IV), (iii) cystic periventricular leukomalacia (cPVL), duration of non-invasive respiratory support (hours), duration of oxygen therapy (hours), bronchopulmonary dysplasia (BPD) diagnosed as oxygen requirement at 36 weeks (mild-moderate-severe),[12,13] and mortality in the DR or before discharge from the hospital.

Pulmochart software (Advanced Life Diagnositcs, Weener, Germany) was used for analysing recorded data. All physiological parameters were analysed manually breath-to-breath by three researchers according to previous described methods.[14] All PPV inflations, including those with integrated spontaneous breaths, were included. Spontaneous breaths on CPAP were excluded from the analyses.

Statistical analyses

A review of previous recordings in Leiden showed the median (IQR) % of Vte in the range 4–8 ml/kg during PPV at birth was 25% (5–45%) with a visible RFM. When developing the study protocol, only one small feasibility study in infants < 32 weeks' gestation using RFM visible or non-visible was available. In that study, Vte > 8 mL/kg was reduced by 19% when the RFM was visible.[9] Therefore, to detect an increase in percentage of inflations within the target range from 25% to 35% with a power of 80% and an error of 5% (two-tailed test), we calculated 286 infants were required in total.

Statistical tests for analysis

Categorical data were analysed using a Chi-square test or Fisher exact test and presented as n (%). Continuous data were judged for normality by inspecting the histograms and presented as median

(IQR) or mean ± SD, analysed using the Mann-Whitney test or two-tailed t-test, as appropriate. To minimise bias in variation in duration of PPV between infants, we calculated the percentage of inflations within the target range per infant per group and reported the median (IQR) percentage of inflations within the target range per group. In addition, we calculated the mean Vte per infant and reported the median (IQR) of all mean Vtes per infant per group. We used the Kolmogórov-Smirnov statistic as a global measure of discrepancy between the distributions of all the Vtes of the two groups. We used permutation testing to compute the associated p-value. All statistical analyses were performed with IBM SPSS Statistics V.25 (IBM Software, Chicago, Illinois, USA, 2016), except for the distribution of Vte and the difference in distribution between infants with and without IVH and/or cPVL, which were analysed with R, V.3.5.0.[15]

Data and safety monitoring committee (DSMB)

A DSMB was established prior to the trial consisting of 1 neonatologist, 1 paediatrician, and 1 biostatistician. A priori stopping rules concerning safety and futility were established, but not for efficacy. Interim analysis was planned after 50% were recruited. The trial was temporarily halted in November 2017 after the interim analysis. Based on the criterion of futility, the DSMB recommended the trial be stopped. The steering committee decided to continue the trial and reach full recruitment for the following reasons: (i) There were no safety concerns and no extra interventions or procedures performed on study infants i(i) At the time the recommendation of the DSMB became available, recruitment was already at 75% of planned, (iii) The presence of a learning curve in using the RFM was suspected and continuing recruitment allowed for an assessment of changes in performance as centres gained experience, (iv) Full recruitment also provided an opportunity to better answer secondary outcome questions. The DSMB had no objection to continuing the trial. Recruitment was restarted after local IRBs approval of the amendment and full recruitment was reached in May 2019.

Results

A total of 579 infants were eligible, of whom 169 were not approached (Fig. 1). A total of 410 infants were randomised with

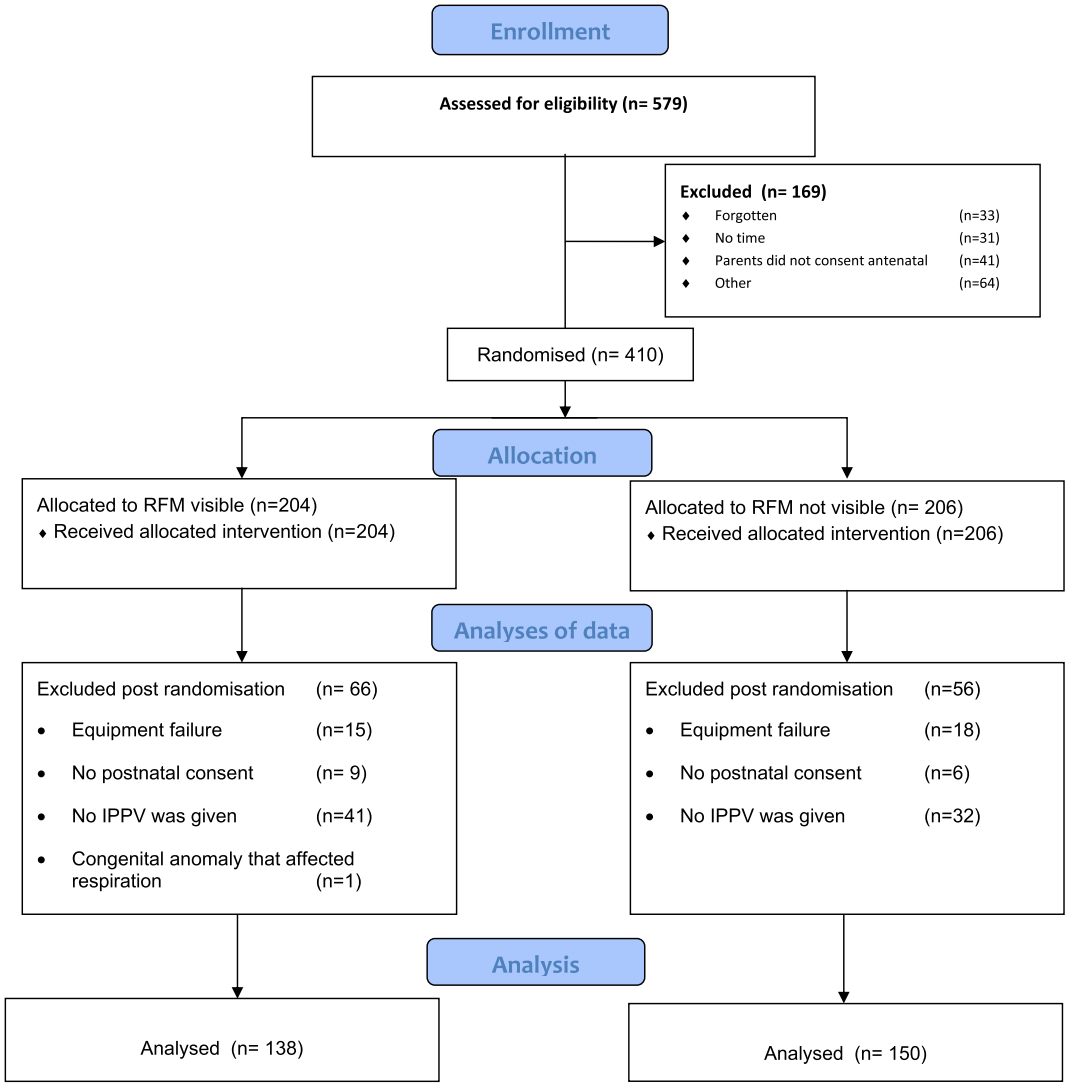


Fig. 1 – CONSORT Flow chart.

Table 1 – Demographic and clinical characteristics.

Characteristics	RFM visible N = 138	RFM non-visible N = 150	p-value
Gestational age in weeks, median (IQR)	$26^{+2}(25^{+2}–27^{+1})$	$26^{+2}(25^{+4}–27^{+1})$	0.900
Birth weight in grams, mean ± SD	822 (187)	823 (195)	0.983
Male, n (%)	74 (53.6)	83 (55.3)	0.771
Twins, n (%)	36 (26.1)	48 (32.0)	0.492
IUGR, n (%)	26 (18.8)	26 (17.4)	0.760
PPROM, n(%)	27 (19.6)	39 (26.0)	0.194
Clinical chorioamnionitis, n (%)	14 (10.1)	15 (10.0)	0.967
Histologic chorioamnionitis, n (%)	20 (14.6)	16 (10.7)	0.500
Antenatal corticosteroids			0.295
complete course, n (%)	97 (70.3)	109 (73.2)	
incomplete course, n (%)	29 (21.0)	22 (14.8)	
Caesarean delivery, n (%)	98 (71.0)	102 (68.0)	0.579
Apgar score 1 min, median (IQR)	4 (3–6)	4 (2–6)	0.698
Apgar score 5 min, median (IQR)	7 (6–8)	7 (6–8)	0.703
Apgar score 10 min, median (IQR)	8 (7–9)	9 (8–9)	0.220
Enrolled in other DR studies, n, (%)	55 (40.7)	66 (44.2)	0.803
Number of resuscitation team members, median (IQR)	3 (2–4)	3 (2–5)	0.179
Grade of resuscitator			0.510
registrar, n (%)	27 (19.7)	24 (16.1)	
neonatal fellow, n (%)	45 (32.8)	58 (38.9)	
neonatologist, n (%)	65 (47.4)	67 (45.0)	
Supervisor present, n (%)	109 (79.6)	121 (81.2)	0.726

IUGR = intra-uterine growth restriction (according to local guidelines), PPROM = preterm premature rupture of membranes, supervisor is defined as an extra neonatal fellow or attending present besides the resuscitator.

204 allocated to the RFM visible group and 206 infants to the RFM non-visible group. After post randomisation exclusions (Fig. 1), 138 infants in the visible and 150 in the non-visible group were analysed.

Demographic and clinical characteristics of the mothers and infants were similar in both groups (Table 1). There were no significant differences in number, experience or grade of the staff present between groups (Table 1).

A total of 51,352 inflations were analysed, with 25,432 in the visible and 25,920 in the non-visible group. The median number of inflations per infant was not significantly different between groups (Table 2).

Primary outcome

The median (IQR) percentage of inflations delivered with Vte within the target range in the visible group was not significantly different from the non-visible group (30.2 (18–41.6)% vs. 30.7 (15.8–43.4)%; p = 0.896; Table 2).

Secondary outcomes: RFM measurements

All other prespecified characteristics and quality of PPV (Table 2), and occurrence of other interventions (Table 2), were not significantly different between groups. The median of the mean Vte in the visible group was lower when compared to the non-visible group, but this was not statistically significant (5.1 (4.0–7.1) mL/kg vs. 5.9 (4.2–8.4) mL/kg; p = 0.057) (Table 2, Fig. 2). There was no significant difference in the distribution of Vte (p = 0.518) (supplement 1). SpO_2, HR and FiO_2 during the first 10 minutes were not significantly different (Table 2).

Secondary outcomes: Clinical measurements

There were no significant differences in the prespecified clinical measurements and outcomes between groups, except for IVH (table 3). The incidence of IVH all grades was significantly lower in the visible group when compared to the non-visible group (26.1% vs. 36.9%; RR 71 (0.50–1.00); p = 0.049), but rates of severe IVH were not significantly different (5.8% vs. 6.7%; RR 0.87 (0.35–2.12); p = 0.75). The combination of the presence of IVH and/or cystic PVL occurred less often in the visible group (26.7% vs. 39.0%; RR 0.68 (0.48–0.97); p = 0.028).

Post hoc analyses

Post-hoc analysis did not show significant differences between the two groups in the following subgroups: 24–25 weeks and 26–27 weeks of gestation, before and after the interim analysis, infants with and without IVH and/or cPVL.

The percentage of inflations with Vte within the target range between infants of 24–25 weeks and 26–27 weeks was not significantly different (30 (11–52)% vs. 30 (18–42)%; p = 0.98), nor was the median Vte (6.1 (4.0–8.1) mL/kg vs. 5.3 (4.1–7.5) mL/kg; p = 0.41).

The percentage of inflations with Vte within the target range before and after the interim analysis was not significantly different (before 31 (18–43)% vs. after 27 (16–44)%; p = 0.392), while the median Vte was significantly higher after the interim analysis (before 5.2 (4.0–7.2) mL/kg vs. after 6.6 (4.5–8.5) mL/kg; p = 0.009).

The percentage of inflations with Vte within the target range between infants with and without IVH and/or cPVL was not significantly different (32 (16–42)% vs. 30 (18–43)%; p = 0.86), nor was the median Vte (5.3 (3.9–7.7) mL/kg vs. 5.6 (4.1–7.5) mL/kg; p = 0.54).

Discussion

In this trial the use of a RFM to guide mask ventilation during stabilisation of extremely preterm infants at birth did not lead to a higher

Table 2 – Delivery room management.

(51352 inflations)	RFM visible N = 138 (25432 inflations)	RFM non-visible N = 150 (25920 inflations)	p-value
RFM measurements			
PPV inflations per infant analysed, median (IQR)	137 (78–261)	136 (59–240)	0.324
Ventilation rate, median (IQR)	54 (45–65)	55 (46–65)	0.954
Duration of PPV (sec), median (IQR)	184 (101–331)	170 (82–292)	0.242
Duration of Vte > 8 ml/kg (sec) , median (IQR)	34 (10–75)	38 (10–78)	0.932
PEEP cm H_2O, median (IQR)	6 (5–7)	6 (5–7)	0.854
Peak inflating pressure cm H_2O, median (IQR)	25 (23–27)	25 (23–26)	0.883
Mean Vte ml/kg per infant, median (IQR)	5.1 (4.0–7.1)	5.9 (4.2–8.4)	0.057
% Vte < 4 ml/kg, median (IQR)	40.7 (20.5–62.4)	34.1 (18.5–52.6)	0.094
% Vte 4–8 ml/kg, median (IQR)	30.2 (18.0–41.6)	30.7 (15.8–43.4)	0.896
% Vte > 8 ml/kg, median (IQR)	20.0 (7.2–41.1)	25.6 (9.6–47.8)	0.141
% of time leak > 60% during PPV per infant, median (IQR)	17.4 (7.2–33.3)	13.6 (3.7–32.1)	0.126
% leak per infant, median (IQR)	24.9 (13.6–39.2)	20.7 (12.3–39.6)	0.350
% of inflations with airway obstruction per infant, median (IQR)	0 (0–0)	0 (0–0)	0.346
Minute ventilation (ml/min), median (IQR)	280 (181–360)	303 (213–387)	0.142
DR interventions			
Mask adjustment/ Reposition airway per infant, median (IQR)	3 (1–7)	3 (1–6)	0.439
Suctioning / Open mouth per infant, median (IQR)	1 (0–2)	0 (0–2)	0.078
Pressure adjustments per infant, median (IQR)	2 (1–3)	2 (1–3)	0.109
PIP adjustments, median (IQR)	1 (0–2)	1 (0–1)	0.063
PEEP adjustments, median (IQR)	1 (0–1.25)	1 (0–1)	0.467
Alternative airway			
Intubation within first 10 min, n (%)	16 (12)	21 (14)	0.542
Intubation in the DR, n (%)	47 (34.1)	54 (36.2)	0.699
Surfactant administration, n (%)	10 (7.2)	16 (10.7)	0.272
Cardiac resuscitation, n (%)			0.569
Chest compressions	2 (1.4)	3 (2.0)	
Adrenaline	1 (0.7)	1 (0.7)	
Physiological measurement			
SpO_2, median (IQR)			
Average first 5 min	59 (46–71)	63 (52–72)	0.107
Average 3–10 min	84 (74–89)	85 (75–90)	0.656
Heart rate, median (IQR)			
Average first 5 min	117 (100–134)	117 (97–131)	0.806
Average 3–10 min	144 (130–156)	143 (127–158)	0.847
FiO_2, median (IQR)			
Average first 5 min	47 (35–61)	47 (37–61)	0.676
Average 3–10 min	51 (36–74)	49 (36–69)	0.434

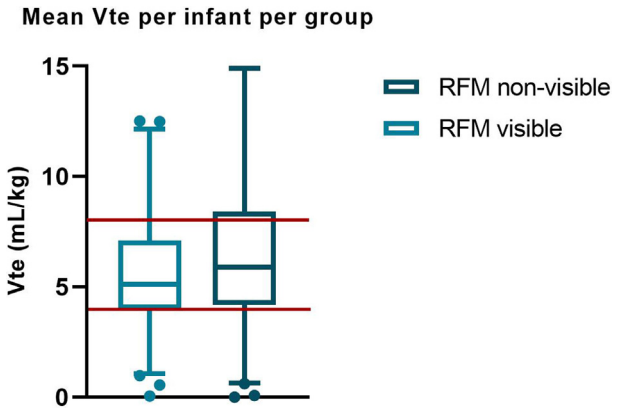


Fig. 2 – Distribution of Vte per infant. Median (IQR) Vte in mL/kg (y-axis) for both groups (x-axis). The horizontal red lines delineate the target range of Vte during positive pressure ventilation.

percentage of Vte within a target range (4–8 ml/kg) during PPV. No significant differences were found between the groups in the characteristics of PPV, the quality of ventilation or any changes the caregivers might have made. The direct effect of PPV on SpO_2 and HR was similar between the groups. This implies that adding a RFM for direct feedback did not change the ventilation given to extremely preterm infants at birth.

This result is in contrast to the beneficial effect of using a RFM reported in manikin, animal or small clinical studies.[9,10] There are several differences in the studies that have to be taken into consideration when comparing the results. As this was a multicentre study, local practices were followed and training in using the RFM was left to the experts in the centre, which could contribute to a larger variability in effect than in a single centre study. Nevertheless, there were no important differences in primary or secondary outcomes between NICUs (data not shown).

To minimise bias in variation in duration of PPV between infants, we calculated the percentage of inflations per infant per group, while

previous studies[9,10] reported the total percentage per group. However, when using the total percentage of inflations with the Vte within a target range of each group, only a small difference in favour of the RFM visible group was found (30.5% vs. 28.9%; p < 0.001). In contrast to Schmolzer et al.,[9] we did not observe fewer intubations in the DR when using a RFM. In an unblinded trial, the outcome of intubations in the DR is susceptible to bias. Although no difference between the groups were observed, less airway obstruction occurred in our study when compared to previous studies.[9,10] One explanation may be that different definitions of obstruction have been used and our definition may have not accounted for the compressive volume of the oropharynx.[16,17]

There are different explanations for why this study was unable to demonstrate a difference and it is difficult to know which might have contributed. It is possible that, despite the training and instructions given, caregivers inexperience with the RFM led to their inability to use it effectively. In a sub-study of this trial, caregivers at two participating centres wore an eye-tracking equipment during the resuscitation, which demonstrated that caregivers did frequently look at the RFM.[18] Unfortunately, this study does not inform us on which RFM variables caregivers focused. It is possible that caregivers saw the RFM data, but familiar parameters, such as chest rise, SpO_2 and HR, were given greater consideration in decisions regarding PPV. Although manikin studies demonstrated that using RFM to guide PPV during simulated neonatal resuscitation improved the performance of caregivers[19–22], resuscitation in real life is more complex and stressful as caregivers assimilate and interpret a constant feedback of different physiological parameters.[23,24] Indeed, Schilleman et al. reported in an observational study that most caregivers did not use the RFM data in making decisions during neonatal resuscitation.[25] This is supported by our finding that a visible RFM did not lead to more corrective procedures to improve PPV.

Another explanation is that even if caregivers used the RFM data, it is unclear whether changes to settings or mask positioning altered the Vte.[26] Recent observational and experimental studies suggest that the effect of PPV given by the caregiver is largely influenced/-modified by the activity status of the glottis and the presence of breathing.[17,27–31] In the fetal state, the glottis is closed a lot of the time and this can continue after birth. Although we aim to provide tidal ventilation, no air can enter the lung when the glottis is closed until the infant takes a breath.[28] Breathing is frequently present during PPV but often missed by the caregiver, which may contribute to

Table 3 – Clinical outcomes.

NICU	Visible N = 138	Not visible N = 149*	p-value	RR (95 %CI)
Intubation, n (%)			0.937	1.01 (0.89–1.13)
DR	47 (34.3)	54 (36.2)		
NICU < 24 h	26 (20.0)	30 (20.1)		
NICU > 24 h	37 (26.8)	34 (22.8)		
No	28 (20.4)	31 (20.8)		
Time of intubation (days), median (IQR) †	1 (1–2.5)	1 (1–2)	0.489	
Surfactant NICU, n(%)	101 (73.2)	102 (68.9)	0.427	1.06 (0.92–1.23)
Mechanical ventilation, n(%)	105 (76.1)	117 (79.1)	0.547	1.15 (0.65–2.03)
Duration mechanical ventilation (days), median (IQR) †	10 (4–25)	8 (4–19.5)	0.199	
Non-invasive ventilation, n(%)	131 (88.5)	124 (89.9)	0.715	0.87 (0.41–1.84
Duration non-invasive ventilation (days), median (IQR) †	43 (31–57.8)	44 (26–58)	0.371	
O2 therapy NICU, n(%)	131 (94.9)	143 (97.3)	0.303	1.91 (0.55–6.68)
Duration O2 therapy (days), median (IQR) †	44 (20–78)	37 (10–75)	0.231	
Nitric oxide treatment, n (%)	12 (8.7)	17 (11.5)	0.435	0.76 (0.38–1.53)
BPD, n (%)			0.518	1.06 (0.85–1.31)
Mild	32 (24.2)	26 (17.4)		
moderate	8 (6.1)	10 (6.7)		
severe	30 (22.7)	41 (27.5)		
Dexamethasone for BPD n (%)	44 (32.6)	44 (29.5)	0.577	1.10 (0.78–1.56)
Pneumothorax, n (%)	6 (4.4)	11 (7.4)	0.283	0.59 (0.23–1.56)
Pulmonary Interstitial Emphysema, n (%)	12 (8.8)	7 (4.7)	0.168	1.86 (0.76–4.60)
Pulmonary haemorrhage with acute respiratory deterioration, n (%)	9 (6.6)	6 (4.0)	0.335	1.63 (0.60–4.46)
Circulatory support (inotropes and/or fluid bolus in first 3 days	42 (30.4)	54 (36.2)	0.298	0.84 (0.60–1.17)
PDA receiving treatment, n (%)			0.944	1.00 (0.78–1.27)
Medical	57 (41.3)	60 (40.3)		
Surgical	8 (5.8)	10 (6.7)		
IVH, all grades, n (%)	36 (26.1)	55 (36.9)	0.049	0.71 (0.50–1.00)
IVH, grade 3 or 4, n (%)	8 (5.8)	10 (6.7)	0.750	0.87 (0.35–2.12)
Cystic PVL, n (%)	1 (0.7)	5 (3.4)	0.216	0.22 (0.03–1.83)
IVH and/or cPVL, n (%)	36 (26.7)	57 (39.0)	0.028	0.68 (0.48–0.97)
ROP, n (%)	9 (6.7)	15 (10.3)	0.280	0.65 (0.29–1.43)
NEC, n (%)	17 (12.3)	13 (8.8)	0.339	1.39 (0.70–2.76)
Mortality in DR, n (%)	0 (0)	1 (0.7)	1.00	1.00 (0.99–1.02)
Mortality before discharge, n (%)	21 (15.2)	24 (16.0)	0.855	0.95 (0.56–1.63)

* 149 infants are included in the clinical outcomes. Only for intubation are 150 infants included as 1 infant died in the delivery room.
† Only infants included receiving corresponding therapy.

augment, counteract or diminish the volume delivered during PPV. This probably explains why some studies show breathing was often more effective in aerating the lung than inflations given by the caregiver.[25,27,32]

All centres used the ALD resuscitation monitor and although we aimed to design an interface where the information displayed was easy to interpret, human factors and the cognitive requirements were not taken into consideration during development. In addition, we chose a Vte target range of 4–8 mL/kg as at the time of starting the trial this was suggested.[11] However, there is still uncertainty what Vte is necessary for lung aeration and it is likely to change with time and breathing. Linde et al. reported that during PPV in apnoeic term infants higher Vte's were used.[33] The recommendation of 4–8 mL/kg is largely based on ventilation via an endotracheal tube. The compressive gas volume of the mask and nasopharynx probably needs to be considered during mask ventilation.

Although this study was not designed to demonstrate differences in clinical outcomes, we observed significantly lower rates of IVH and/or cPVL in the RFM visible group. Previous studies reported an association between high tidal volumes and hypoxia in the first minutes after birth with increased risk for IVH.[34,35] However, in our study the Vte and SpO_2 were similar between the groups with or without IVH and/or cPVL. We did not measure end-tidal CO_2 ($etCO_2$) but Tamura et al. showed that high $etCO_2$ levels in the first minutes after birth were associated with the occurrence of IVH.[36] $EtCO_2$ is largely determined by the degree of lung aeration,[37] minute volume and an expiratory time sufficient to form an expiratory CO_2 plateau. The minute volume of PPV given was not significantly different between groups, although the minute volume of spontaneous breathing combined with PPV was not calculated. Nevertheless, as no differences in parameters provided by RFM were observed that could explain the difference in IVH and/or cPVL, it is possible that this finding occurred by chance, requiring further investigation.

The strength of this study is that over 50,000 inflations were investigated in 288 infants, given by caregivers in different hospitals over the world. It is known that local guidelines vary between hospitals and compliance with protocols differs, but the findings of this multicentre study may be more generalisable than previous trials.[9,10] In addition, the blinded manual analysis of each breath adds to the validity of the data analysis. Automated analysis can be misleading when spontaneous breathing interferes with the flow waves of inflations given, which occurs frequently at birth.[25,32]

A limitation of the study is that we did not control for the training performed in the hospitals participating and no standard operating procedure was established. Although we could not observe significant differences in primary outcome between centres, it is possible that a more structured training in using the RFM could have affected the results. In addition, as the monitor screen was visible from the start of birth in the visible group, this could have influenced the decision for providing PPV, although this was not significant (no iPPV provided: visible 41 (20.1) vs non-invisible 32 (15.5), p = 0.227). Moreover, the measured birth weight was used to calculate tidal volumes instead of the estimated birth weight based on ultrasound measurements. This could have led to minimal variance in tidal volumes, although this is equally distributed in both groups. Another limitation is that almost seven years were need to complete recruitment and it is possible that caregivers were subject to a Hawthorne effect. Over time, the learning effect of using RFM during PPV could have improved the performance of caregivers providing PPV in the RFM blinded group.

In conclusion, a RFM during PPV of extremely preterm infants at birth, as compared to no RFM, did not increase the percentage of inflations within a target range. The PPV given, the quality, the corrections made, and the clinical responses were not influenced by the RFM, indicating that the availability of data from the monitor did not change the performance of caregivers. Further studies are needed to investigate whether a more structured training and/or different monitor interface could lead to different results in all infants needing resuscitation.

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Declaration of Competing Interest

AtP, OK, MV, GL contributed to the conception and design of the study and all authors participated in reviewing the protocol. All authors were involved in coordinating the study, training the clinicians and collecting the data. HvZ, KK, JV analysed the data. HvZ and KK interpreted the data and wrote the first draft of the manuscript under supervision of AtP. All authors participated in reviewing and editing and all approved the final manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2021.07.012.

REFERENCES

1. Trevisanuto D, Satariano I, Doglioni N, et al. Changes over time in delivery room management of extremely low birth weight infants in Italy. Resuscitation 2014;85:1072–6.
2. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med 2010;362:1970–9.
3. Polglase GR, Miller SL, Barton SK, et al. Respiratory support for premature neonates in the delivery room: effects on cardiovascular function and the development of brain injury. Pediatr Res 2014;75:682–8.
4. Perlman JM, Wyllie J, Kattwinkel J, et al. Part 7: Neonatal Resuscitation: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations (Reprint). Pediatrics 2015;136: S120–66.
5. Schmölzer GM, Kamlin OC, O'Donnell CP, Dawson JA, Morley CJ, Davis PG. Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room. Arch Dis Child Fetal Neonatal Ed 2010;95:F393–7.
6. Brugada M, Schilleman K, Witlox RS, Walther FJ, Vento M, Te Pas AB. Variability in the assessment of 'adequate' chest excursion during simulated neonatal resuscitation. Neonatology 2011;100:99–104.
7. Dawson JA, Schmölzer GM, Kamlin CO, et al. Oxygenation with T-piece versus self-inflating bag for ventilation of extremely preterm infants at birth: a randomized controlled trial. J Pediatr 2011;158. pp. 912–8.e1-2.

8. van Vonderen JJ, van Zanten HA, Schilleman K, et al. Cardiorespiratory Monitoring during Neonatal Resuscitation for Direct Feedback and Audit. Front Pediatr 2016;4:38.
9. Schmolzer GM, Morley CJ, Wong C, et al. Respiratory function monitor guidance of mask ventilation in the delivery room: a feasibility study. J Pediatr 2012;160:377–81.
10. Sarrato GZ, Luna MS, Sarrato SZ, Perez AP, Chamorro IP, Cano JMB. New Strategies of Pulmonary Protection of Preterm Infants in the Delivery Room with the Respiratory Function Monitoring. Am J Perinatol 2019;36(13):1368–76.
11. Schmölzer GM, Te Pas AB, Davis PG, Morley CJ. Reducing lung injury during neonatal resuscitation of preterm infants. J Pediatr 2008;153:741–5.
12. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163(7):1723–9.
13. Walsh MC, Szefler S, Davis J, et al. Summary proceedings from the bronchopulmonary dysplasia group. Pediatrics 2006;117(3 Pt 2): S52–6.
14. Dekker J, Martherus T, Lopriore E, et al. The Effect of Initial High vs. Low FiO(2) on Breathing Effort in Preterm Infants at Birth: A Randomized Controlled Trial. Front Pediatr 2019;7:504-.
15. R core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing; 2015. https:// www.R- project.org/.
16. Kamlin COF, Schmölzer GM, Dawson JA, et al. A randomized trial of oropharyngeal airways to assist stabilization of preterm infants in the delivery room. Resuscitation 2019;144:106–14.
17. van Vonderen JJ, Kamlin CO, Dawson JA, Walther FJ, Davis PG, te Pas AB. Mask versus Nasal Tube for Stabilization of Preterm Infants at Birth: Respiratory Function Measurements. J Pediatr 2015;167 (1):81–5 e1.
18. Herrick H, Weinberg D, Cecarelli C, et al. Provider visual attention on a respiratory function monitor during neonatal resuscitation. Arch Dis Child Fetal Neonatal Ed 2020;105(6):666–8.
19. Wood FE, Morley CJ, Dawson JA, Davis PG. A respiratory function monitor improves mask ventilation. Arch Dis Childhood Fetal Neonatal Ed 2008;93(5):F380–1.
20. Kelm M, Dold SK, Hartung J, Breckwoldt J, Schmalisch G, Roehr CC. Manual neonatal ventilation training: a respiratory function monitor helps to reduce peak inspiratory pressures and tidal volumes during resuscitation. J Perinat Med 2012;40(5):583–6.
21. Binder C, Schmölzer GM, O'Reilly M, Schwaberger B, Urlesberger B, Pichler G. Human or monitor feedback to improve mask ventilation during simulated neonatal cardiopulmonary resuscitation. Arch Dis Child Fetal Neonatal Ed 2014;99(2):F120–3.
22. Jain D, D'Ugard C, Aguilar A, Del Moral T, Bancalari E, Claure N. Use of a Mechanical Ventilator with Respiratory Function Monitoring Provides More Consistent Ventilation during Simulated Neonatal Resuscitation. Neonatology 2020;117(2):151–8.
23. Schilleman K, Siew ML, Lopriore E, Morley CJ, Walther FJ, Te Pas AB. Auditing resuscitation of preterm infants at birth by recording video and physiological parameters. Resuscitation 2012;83 (9):1135–9.
24. Root L, van Zanten HA, den Boer MC, Foglia EE, Witlox RSGM. te Pas AB. Improving Guideline Compliance and Documentation Through Auditing Neonatal Resuscitation. Front Pediatr 2019;7(294).
25. Schilleman K, van der Pot CJ, Hooper SB, Lopriore E, Walther FJ, te Pas AB. Evaluating manual inflations and breathing during mask ventilation in preterm infants at birth. J Pediatr 2013;162(3):457–63.
26. Yang KC, Te Pas AB, Weinberg DD, Foglia EE. Corrective steps to enhance ventilation in the delivery room. Arch Dis Child Fetal Neonatal Ed 2020;105(6):605–8.
27. van Vonderen JJ, Lista G, Cavigioli F, Hooper SB, te Pas AB. Effectivity of ventilation by measuring expired CO2 and RIP during stabilisation of preterm infants at birth. Arch Dis Child Fetal Neonatal Ed 2015;100(6):F514–8.
28. Crawshaw JR, Kitchen MJ, Binder-Heschl C, et al. Laryngeal closure impedes non-invasive ventilation at birth. Arch Dis Child Fetal Neonatal Ed 2018;103(2):F112–9.
29. Milner AD, Vyas H, Hopkin IE. Efficacy of facemask resuscitation at birth. Br Med J (Clin Res Ed) 1984;289(6458):1563–5.
30. te Pas AB, Kamlin CO, Dawson JA, et al. Ventilation and spontaneous breathing at birth of infants with congenital diaphragmatic hernia. J Pediatr 2009;154(3):369–73.
31. Murthy V, D'Costa W, Shah R, et al. Prematurely born infants' response to resuscitation via an endotracheal tube or a face mask. Early Hum Dev 2015;91(3):235–8.
32. van Vonderen JJ, Hooper SB, Hummler HD, Lopriore E, te Pas AB. Effects of a sustained inflation in preterm infants at birth. J Pediatr 2014;165(5):903–8 e1.
33. Linde JE, Schulz J, Perlman JM, et al. The relation between given volume and heart rate during newborn resuscitation. Resuscitation 2017;117:80–6.
34. Oei JL, Finer NN, Saugstad OD, et al. Outcomes of oxygen saturation targeting during delivery room stabilisation of preterm infants. Arch Dis Child Fetal Neonatal Ed 2018;103(5):F446–54.
35. Mian Q, Cheung PY, O'Reilly M, Barton SK, Polglase GR, Schmölzer GM. Impact of delivered tidal volume on the occurrence of intraventricular haemorrhage in preterm infants during positive pressure ventilation in the delivery room. Arch Dis Child Fetal Neonatal Ed 2019;104(1):F57–62.
36. Tamura K, Williams EE, Dassios T, et al. End-tidal carbon dioxide levels during resuscitation and carbon dioxide levels in the immediate neonatal period and intraventricular haemorrhage. Eur J Pediatr 2020;179(4):555–9.
37. Hooper SB, Fouras A, Siew ML, et al. Expired CO2 levels indicate degree of lung aeration at birth. PLoS One 2013;8(8) e70895.