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Predictors for expired CO_2 in neonatal bag-mask ventilation at birth: observational study

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ABSTRACT

Background Expired carbon dioxide (ECO_2) indicates degree of lung aeration immediately after birth. Favourable ventilation techniques may be associated with higher ECO_2 and a faster increase. Clinical condition will however also affect measured values. The aim of this study was to explore the relative impact of ventilation factors and clinical factors on ECO_2 during bag-mask ventilation of near-term newborns.

Methods Observational study performed in a Tanzanian rural hospital. Side-stream measures of ECO_2, ventilation data, heart rate and clinical information were recorded in 434 bag-mask ventilated newborns with initial heart rate <120 beats per minute. We studied ECO_2 by clinical factors (birth weight, Apgar scores and initial heart rate) and ventilation factors (expired tidal volume, ventilation frequency, mask leak and inflation pressure) in random intercept models and Cox regression for time to ECO_2 >2%.

Results ECO_2 rose non-linearly with increasing expired tidal volume up to >10 mL/kg, and sufficient tidal volume was critical for the time to reach ECO_2 >2%. Ventilation frequency around 30/min was associated with the highest ECO_2. Higher birth weight, Apgar scores and initial heart rate were weak, but significant predictors for higher ECO_2. Ventilation factors explained 31% of the variation in ECO_2 compared with 11% for clinical factors.

Conclusions Our findings indicate that higher tidal volumes than currently recommended and a low ventilation frequency around 30/min are associated with improved lung aeration during newborn resuscitation. Low ECO_2 may be used to identify unfavourable ventilation technique. Clinical factors are also associated with persistently low ECO_2 and must be accounted for in the interpretation.

What is known about the subject?

- ► Expired CO_2 (ECO_2) is low immediately after birth before the lung liquid is cleared.
- ► ECO_2 may serve as a marker for effective ventilations in intubated patients.

What this study adds?

- ► The quality of ventilations are more important than the clinical condition for measured ECO_2 during the first minutes of bag-mask ventilation in newborn resuscitation.
- ► Ventilation frequency around 30/min gives the highest ECO_2.
- ► Tidal volumes of 10–14 mL/kg are associated with the highest ECO_2 and the shortest time to reach ECO_2 >2%.

INTRODUCTION

Around 3%–6% of newborns receive positive pressure ventilation at birth to facilitate transition and establish cardiorespiratory stability.[1–3] Heart rate (HR) response is an important indicator of effective resuscitation,[3 4] but cannot directly assess ventilation. Hooper *et al* found that expired carbon dioxide (ECO_2) indicates degree of lung aeration immediately after birth.[5]

Newborn lungs are liquid filled. Before functional residual capacity is sufficiently established, gas exchange is diffusion limited.[6] To detect ECO_2, liquid must be cleared and air must enter the alveoli. ECO_2 increases rapidly in the first minute of extrauterine life during spontaneous breathing, but slower if positive pressure ventilation is needed.[7–9] Capnography may help identify unfavourable technique and guide ventilations during newborn resuscitation.[10–14] There is currently insufficient evidence that ECO_2 monitoring during newborn resuscitation affects outcome.[3 15] ECO_2 depends, in addition to ventilation, on metabolism and pulmonary circulation.[16]

Optimal ventilation strategies for rapidly establishing effective pulmonary gas exchange in non-breathing newborns have not been fully determined. Recent studies indicate that larger tidal volumes (V_{TE}) than the 4–8 mL/kg currently recommended may cause faster increase in HR.[4 17 18] Guideline recommendations for ventilation frequency vary between

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the USA (40–60/min) and Europe (30/min), and evidence for any recommendation is sparse.[19 20]

In this study, we aimed to explore the relative impact of ventilation factors (V_{TE}, frequency, mask leak and pressure) and clinical factors (birth weight (BW), Apgar scores and initial HR) on ECO_2 during bag-mask ventilation (BMV) in resuscitation of term and near-term newborn infants. Better understanding may improve interpretation of ECO_2 measurements and help determine optimal ventilation strategies.

METHODS

Study design and setting

Observational study performed between 1 March 2013 and 1 June 2017 at Haydom Lutheran Hospital, a rural Tanzanian referral hospital with 4–5000 deliveries annually. The study was part of Safer Births, a research consortium on labour surveillance and newborn resuscitation in low-income settings.[4 21 22] Midwives and nursing students conducted most vaginal deliveries. Newborn resuscitation was mainly the responsibility of midwives.

Data collection, equipment and training

Trained non-medical research assistants observed all deliveries, documented time intervals and recorded perinatal information.[2] A newborn resuscitation monitor developed for research by Lærdal Global Health, Stavanger, Norway was mounted on the wall above all resuscitation tables (23). Each monitor was equipped with a self-inflating bag (230 mL standard or 320 mL Upright bag-mask; Laerdal Medical, Stavanger, Norway) and a dry-electrode ECG sensor to be easily placed around the newborns' trunk. Sensors for side-stream CO_2 (ISA; Masimo, Irvine, California, USA), pressure (Freescale semiconductor, Austin, Texas, USA) and flow (Acutronic Medical Systems, Hirzel, Switzerland) to record ECO_2 and ventilation parameters were placed between the mask and bag; the attachment device added a dead space of 1 mL. The monitors provided HR feedback. ECO_2 and ventilation parameters were not displayed.

The local newborn resuscitation procedure followed the Helping Babies Breathe (HBB) guidelines.[24] HBB was introduced at the study site in 2009. Midwives participated in full-day HBB courses one to two times yearly, and were educated to use clinical signs including chest rise and HR feedback to guide resuscitation. Low-dose, high-frequency skills training as described by Mduma *et al* was encouraged.[22]

Formation of the cohort

We included all live-born newborns with initial HR <120 bpm who had received BMV at birth, and had available HR, ventilation and observational data (figure 1). Our research group recently showed that normal HR is around 120 bpm in the first seconds of life.[25] Low initial HR is a known risk factor for unfavourable outcome.[21] Newborns who received BMV but had HR ≥120 bpm at onset of recording were excluded as these are likely different in pathophysiology and prognosis. Newborns randomised to receive BMV with positive end-expiratory pressure (PEEP) valve in a parallel intervention study were excluded due to potential impact of PEEP on ECO_2.

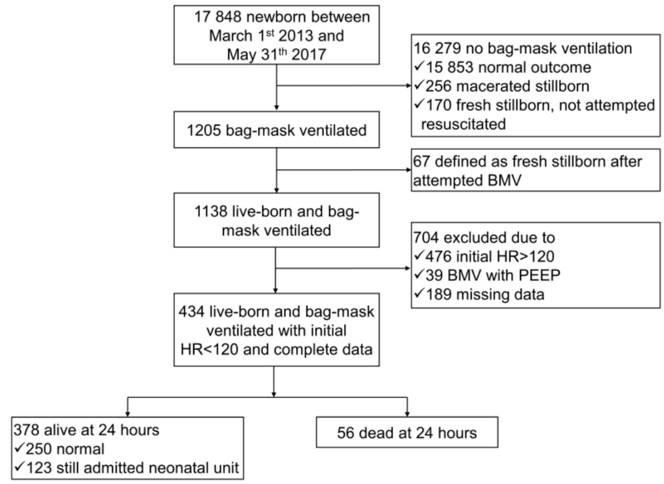

Figure 1 Overall newborn mortality at Haydom Hospital during the study period was 31 per thousand births. Among these, 28 were defined as still births, 13 fresh and 15 macerated. BMV, bag-mask ventilation; HR, heart rate; PEEP, positive end-expiratory pressure.

Outcome and covariates

The primary outcome was the maximum percentage of CO_2 in expired air per ventilation. Secondary outcome was time to ECO_2 >2% from the first BMV.

To characterise assisted ventilations ('ventilation factors'), we used repeated measures for expired V_{TE}, ventilation frequency, peak inflating pressure (PIP) and mask leak smoothed as means per five ventilations. The threshold to detect a ventilation was set to PIP >5 mbar.

As markers of clinical condition ('clinical factors'), we used the initial HR and 5 min Apgar score. Initial HR was defined as the mean of the first five HR values recorded for each newborn. The 5 min Apgar score was selected due to established association with asphyxia.[26] In a sensitivity analysis, we substituted Apgar score at 5 min with 1 min because 5 min score may be affected by treatment.

We also included BW and time as covariates. In the primary analyses, within the first 5 min of ventilation, time was recorded from the first detected ventilation. In the secondary analyses, per ventilation sequences, time was recorded from the first detected ventilation per sequence. We defined a ventilation sequence as continuous BMV with <5 s pause between two ventilations.

V_{TE} >30 mL/kg were considered unlikely to be correct measurements and were excluded. We also excluded individual observations with ventilation frequency >120/min as this is twice the upper limit of recommended ventilation frequency.

Table 1 Baseline characteristics and covariates				
		All newborns (n=17 848)*	**Included newborns (n=434)***	**ICC†**
Delivery mode	Caesarean section	3937 (23%)	215 (50%)	–
	Standard vaginal	13 331 (76%)	194 (45%)	–
	Breech	162 (0.9%)	24 (6%)	–
	Vacuum	39 (0.2%)	1 (0.2%)	–
	Other	14 (0.1%)	–	
Females		8167 (47%)	168 (39%)	–
Gestational age (weeks)		38 (37–40)	38 (37–40)	–
Gestational age <36 weeks		594 (3.3%)	29 (7%)	–
Birth weight (g)		3248 ± 535	3074 ± 593	–
Apgar 1 min		9 (9–9)	6 (5–7)	–
Apgar 5 min		10 (10–10)	10 (8–10)	–
First detected heart rate (bpm)		–	73 ± 21	–
Time from birth to first ventilation (s)		–	112 (78–158)	–
Time from first to last ventilation (s)		–	184 (80–394)	–
Time to ECO_2 >2% (s)		–	10.0 (3.1–34.9)‡	–
No of ventilation sequences		–	5 (2–8)	–
Duration of ventilation sequences (s)		–	29 ± 46§ / 18 (11 - 30)¶	0.15
Expired volume, V_{TE} (mL/kg)		–	7.9 ± 6.4§ / 6.7 (4.1–11.0)¶	0.52
Ventilation frequency (BMVs/min)		–	52 ± 24§ / 47 (38–65)¶	0.62
Mask leak (%)¶		–	44 ± 29§ / 40 (25–59)¶	0.40
Peak inflation pressure (mbar)¶		–	35 ± 11§ / 38 (25–60)¶	0.54
ECO_2 (% of expired air) ¶		–	2.9 ± 2.2§ / 2.9 (1.3–4.1)¶	0.50
Max ECO_2 in first 5 min of BMV		–	7.2 ± 2.8	–
Initial ECO_2		–	0.9 (0.3–3.3)	–

*Frequencies are given in the form of n (%), parameters with skewed distributions are given as median (25th quartile, 75th quartile), normally distributed parameters as mean±SD. For ventilation factors with repeated measurements per newborn, we report both means calculated by unconditional random intercept analysis and medians of medians.
†ICC—intercorrelation coefficient: proportion of total variance assigned to variance between patients.
‡Newborns who had ECO_2 >2% in the first ventilation (n=113) or did not reach threshold (n=23) not included.
§Mean in first 5 min of BMV, SD is given as √total variance where the total variance is the sum of variance between and within patients.
¶Median of medians in first 5 min of BMV.
BMV, bag-mask ventilation; ECO_2, expired carbon dioxide.

Statistical analyses

For cohort and data description, we report percentages, means with SD or medians with IQRs, as appropriate (table 1). For ventilation parameters, we include intercorrelation coefficients due to variation both within and between patients.

We fitted random intercept regression models to study changes in ECO_2 by variations in clinical and ventilation factors for newborns who received BMV. Associations with ECO_2 were not linear for all covariates, thus we performed log transformation for time, and included a quadratic term for V_{TE} and PIP guided by Akaike's information criteria and inspection of the residuals. To compare the effect of covariates measured on different scales, we report beta values per standardised units ((x−mean)/SD) in addition to the measured scale for each covariate and coefficients of determination (R^2 values). R^2 was calculated as the proportional reduction in prediction error variance comparing models with and without the covariate of interest.[27] For closely correlated parameters, we excluded both parameters simultaneously.

The primary analysis was performed in the first 5 min of BMV. Second, we compared the effects per ventilation sequence for newborns who had three or more sequences lasting for more than 10 s to evaluate build-up effects and the impact of pauses. We used Cox regression to study predictors for time from first BMV until ECO_2 reached 2% (≈2 kPa or 15 mm Hg at sea level). ECO_2 threshold was set at 2% as this corresponds well with changes on the colorimetric CO_2 detectors[11] and the ECO_2 level found to be most predictive for HR >60 bpm.[28] Kruskal-Wallis test was used to compare clinical and ventilation factors in three groups of infants differing by when ECO_2 >2% was achieved: never, during ventilation or spontaneously.

Data analysis was performed using MATLAB (MathWorks, Natick, Masschusetts, USA) and Stata SE V.14.2 (StataCorp, College Station, Texas, USA). We used a purposeful selection approach to build regression models; only significant covariates ($p<0.05$) were included in the final models.

Patient and public involvement

The study was performed in an area with high illiteracy rate, and patients and public were not directly involved in the planning of the study. Oral feedback from patients and personnel were taken into account for solving practical issues concerning data collection during the study period.

Ethical considerations

All women were informed, but consent was not considered necessary by the ethical committees.

RESULTS

During the study period, 17484 babies were born in the hospital; 6.9% received BMV (figure 1). Among 434 included newborns, 400 had a minimum of one ventilation sequence that lasted for more than 10s (baseline data in table 1).

Predictors of ECO_2 during first 5 min

Both clinical and ventilation factors were significantly associated with ECO_2, but ventilation explained substantially more of the variance than clinical factors (R^2 30.8% vs 10.9%); V_{TE} was the strongest single predictor (table 2). The association between V_{TE} and ECO_2 was positive and close to linear for V_{TE} <10mL/kg, levelling off at 10–20mL/kg and negative >20mL/kg (figure 2A). Mask leak and V_{TE} were negatively correlated, and together explained 23% of the variance in ECO_2. Low ventilation frequency around 30/min was associated with

Table 2 Linear random intercept model for predictors of expired carbon dioxide (ECO_2) in the first 5 min of bag-mask ventilation

Covariates		Univariate model*			Multivariate model			
		Coefficient (95% CI)	P value	R^2 (%)	Coefficient (95% CI)	P value	R^2 (%)	R^2 (%)
ECO_2 (unconditional)		2.90 (2.75 to 3.05)						
Ventilation characteristics	*Expired tidal volume (V_{TE})* Per mL/kg increase Per standardised unit	0.37 (0.33 to 0.42) 2.37 (2.10 to 2.65)	<0.001	19.3	0.32 (0.27 to 0.37) 2.02 (1.71 to 2.33)	<0.001	23.1†	30.8
	$(V_{TE})^2$ Per 100 $(mL/kg)^2$ increase Per standardised unit	−0.86 (−1.0 to 0.7) −1.29 (−1.53 to −1.06)	<0.001		−0.78 (−0.9 to −0.6) −1.17 (−1.40 to −0.94)	<0.001		
	Mask leak Per 10% increase Per standardised unit	−0.30 (−0.33 to −0.27 −0.85 (−0.87 to −0.84)	<0.001	16.1	−0.056 (−0.098 to −0.014) −0.16 (−0.29 to 0.42)	0.009		
	Ventilation frequency Per 10 bpm increase Per standardised unit	−0.17 (−0.23 to −0.11) −0.40 (−0.55 to −0.26)	<0.001	7.5	−0.16 (−0.19 to −0.12) −0.37 (−0.45 to −0.28)	<0.001	16.1‡	
	Peak inflation pressure (PIP) Per 10 mbar increase Per standardised unit	0.41 (0.16 to 0.67) 0.46 (0.18 to 075)	0.001	1.1	0.24 (0.064 to 0.29) 0.27 (0.071 to 0.46)	0.008	−0.3	
	$(PIP)^2$ Per 10 $mbar^2$ increase Per standardised unit	−0.60 (−0.87 to −0.33) −0.61 (−0.88 to −0.33)	<0.001		−0.47 (−0.64 to −0.29) −0.47 (−0.65 to −0.29)	<0.001		
Clinical factors	*Birth weight* Per kg increase Per standardised unit	0.78 (0.51 to 1.04) 0.46 (0.30 to 0.62)	<0.001	4.4	0.81 (0.58 to 1.03) 0.48 (0.34 to 0.61)	<0.001	6.8	10.9
	Initial heart rate Per 10 bpm increase Per standardised unit	0.081 (0.012 to 0.15) 0.17 (0.024 to 0.31)	0.022	0.6	0.089 (0.034 to 0.14) 0.19 (0.070 to 0.30)	0.002	1.3	
	5 min Apgar score Per one unit increase Per standardised unit	0.054 (−0.021 to 0.13) 0.11 (−0.043 to 0.26)	0.16	0.3	0.14 (0.068 to 0.22) 0.29 (0.14 to 0.44)	<0.001	2.9	
Log2 of time in seconds Per unit increase Per standardised unit		0.33 (0.28 to 0.38) 0.64 (0.54 to 0.73)	<0.001	2.0	0.15 (0.12 to 0.19) 0.29 (0.23 to 0.36)	<0.001	0.9	0.9
Random-effects parameters					Var (_cons) 1.53 (1.31 to 1.77)§ Var (Residual) 1.53 (1.34 to 1.74) ICC 0.50			

*Intercorrelation coefficient (ICC) varied between 0.47 and 0.56 for all covariates.
†V_{TE} and mask leak were correlated (Spearman's rho −0.65). Excluding V_{TE} from the model, beta value for mask leak decreased from −0.056 (−0.098 to −0.014) to −0.28 (−0.31 to −0.24). R^2 for V_{TE} alone excluding mask leak from the model was 21.9%. R^2 for mask leak excluding V_{TE} was 17.1%.
‡Interaction term for V_{TE} and frequency was significant with beta=−0.015 (−0.020 to −0.0091), p<0.001, the model is displayed without this term for interpretability. V_{TE} and frequency were still significant in the model including the interaction term.
§R^2 for the total model: 36.6%.

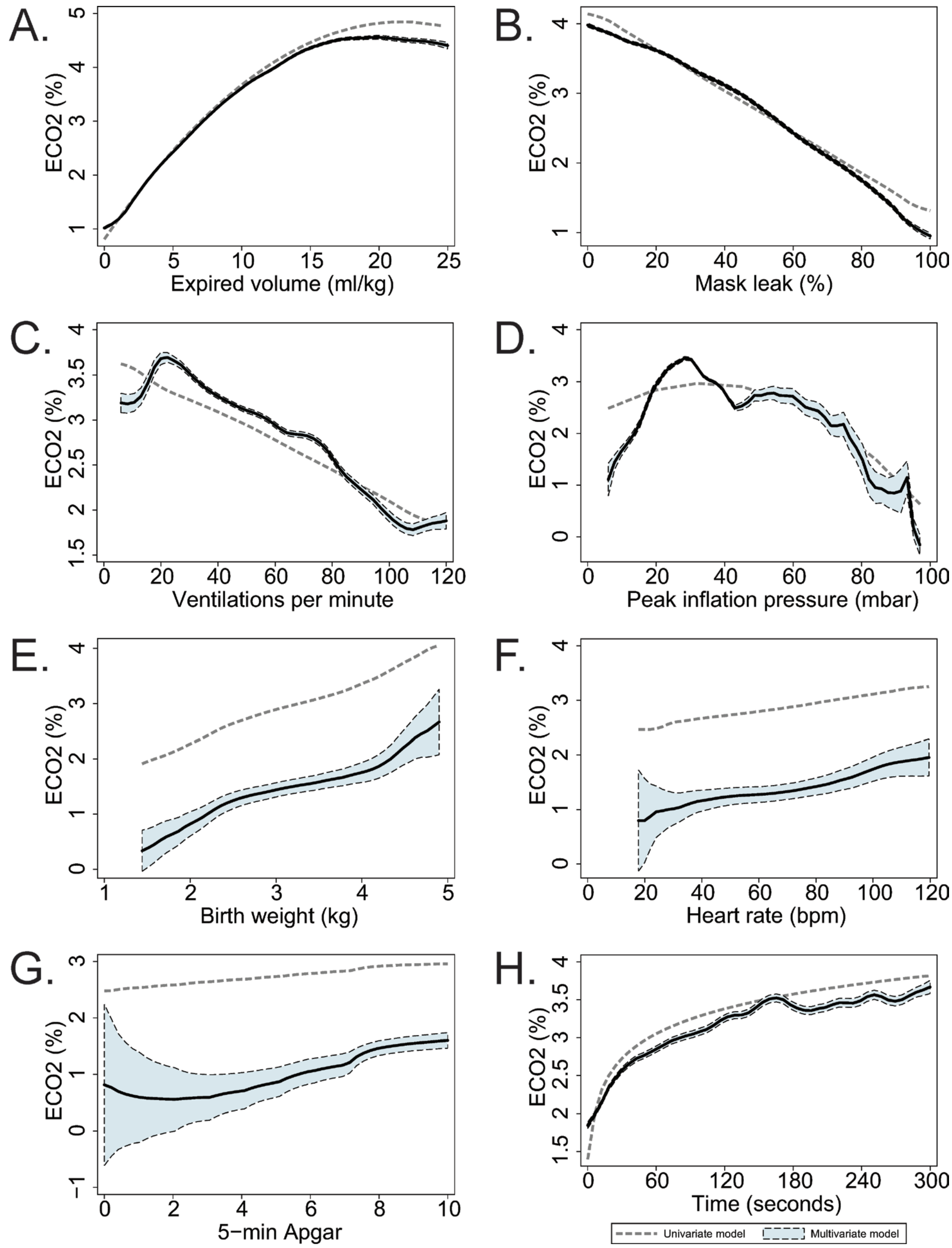

Figure 2 ECO_2 by covariates. Smoothed local polynomial plots for predicted values of expired carbon dioxide (ECO_2) per covariate in univariate (dashed, grey line) and multivariate model (solid, black line). The graphs display ECO_2 versus (A) expired tidal volume (V_{TE}, mL/kg), (B) mask leak (percentage leak), (C) ventilation frequency (ventilations per minute), (D) peak inflation pressure (PIP, mbar), (E) birth weight (kg), (F) initial heart rate (beats per minute), (G) 5 min Apgar score and (H) time (seconds). Table 2 display effect measures (beta coefficients), p values and explained variance (R^2) for the regression models.

the highest ECO_2 (figure 2C). PIP <15 or >60 mbar were associated with low ECO_2 (figure 2D). ECO_2 increased rapidly in the first minute of BMV, V_{TE} increased and mask leak decreased simultaneously (figure 3). BW and initial HR were positively associated with ECO_2 in univariate and multivariate models, 5 min Apgar score only in the multivariate model (table 2, figure 2E–G).

Predictors for ECO_2 by ventilation sequence

Analysing the first three ventilation sequences with duration >10 s (online supplementary appendix table S1 A–C) gave similar results as the primary analysis, with V_{TE} as the strongest predictor. ECO_2 increased significantly with time in the first two ventilation sequences, but not in the third (online supplementary appendix figure S1).

Predictors for time to reach threshold

The Cox model found higher V_{TE} up to 14 mL/kg to be associated with shorter time to reach ECO_2 >2% (table 3). Higher 5 min Apgar score, initial HR, BW and PIP were also associated with shorter time to reach ECO_2 >2%.

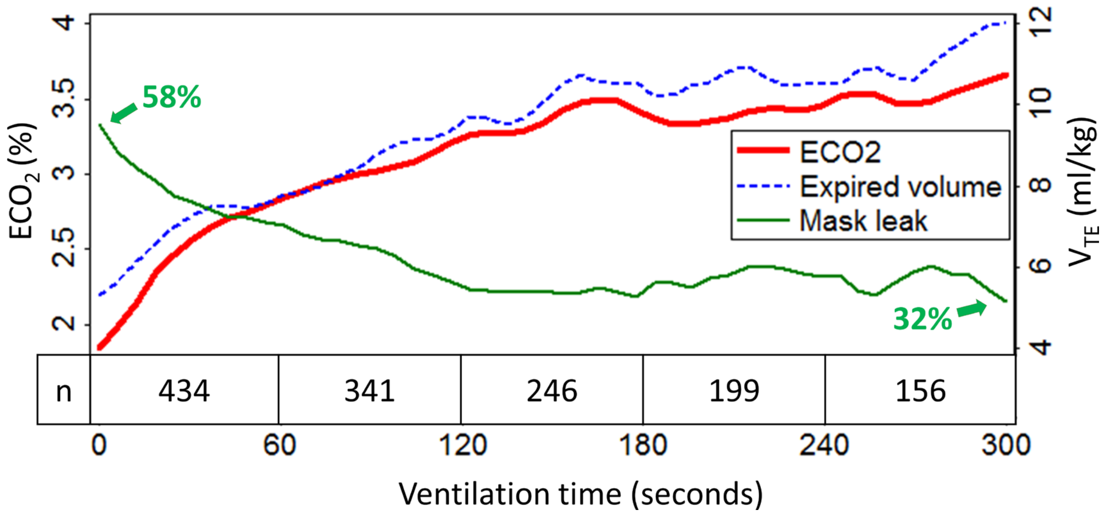

Figure 3 Change in expired carbon dioxide (ECO_2), expired volume and mask leak by time the figure illustrates trends for changes in ECO_2 (red, solid line), V_{TE} (blue, dashed line) and mask leak (green, dashed line) by time. The graphs are smoothed local polynomial plots. The integrated table displays the number of newborns (n) who received ventilations in each minute since start of ventilations.

Interactions and stratified analyses

In the primary analysis, we found a significant interaction for V_{TE} and frequency. We found no relevant differences stratified by BW ≥2500 g versus <2500 g, initial HR ≥60 versus <60 bpm, vaginal delivery versus Caesarean section or for newborns ventilated within versus after 60 s from birth (data not shown). Substituting V_{TE} and ventilation frequency with respiratory minute volume, we found a non-linear positive association between ECO_2 and minute volumes (online supplementary appendix

Table 3 Cox regression for time to ECO_2 >2% (n=321)*

	Univariate model		Multivariate model†‡	
	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Expired tidal volume (V_{TE})				
Per 1 mL/kg increase	1.18 (1.11 to 1.24)	<0.001	1.22 (1.15 to 1.29)	<0.001
Per standardised unit	1.33 (1.18 to 1.50)		3.75 (2.56 to 5.48)	
$(V_{TE})^2$§				
Per unit increase	0.99 (0.99 to 0.99)	<0.001	0.99 (0.99 to 1.0)	<0.001
Per standardised unit	1.16 (1.02 to 1.31)		0.34 (0.22 to 0.52)	
Peak inflation pressure				
Per 10 mbar increase	1.24 (1.15 to 1.35)	<0.001	1.32 (1.21 to 1.43)	<0.001
Per standardised unit	1.28 (1.17 to 1.40)		1.36 (1.24 to 1.50)	
Birth weight				
Per kg increase	1.32 (1.09 to 1.59)	0.004	1.42 (1.17 to 1.72)	0.001
Per standardised unit	1.18 (1.05 to 1.32)		1.23 (1.10 to 1.38)	
Initial heart rate				
Per 10 bpm increase	1.08 (1.02 to 1.14)	0.004	1.08 (1.02 to 1.14)	0.006
Per standardised unit	1.18 (1.05 to 1.32)		1.17 (1.05 to 1.30)	
Apgar at 5 min				
Per unit increase	1.10 (1.04 to 1.16)	0.001	1.17 (1.11 to 1.24)	<0.001
Per standardised unit	1.23 (1.09 to 1.38)		1.42 (1.25 to 1.61)	

*Among n=434 included newborns, 113 were censured before analysis due to ECO_2 >2% in the first ventilation, 321 were included in the Cox regression, 23 never reached ECO_2 >2%.
†Hazard Ratios were not proportional for V_{TE} alone, including a quadratic term gave acceptable fit in the multivariate model.
‡Mask leak was significant (p<0.001) in univariate model, but not in multivariate model (p=0.26) including V_{TE} due to correlation with volume. Taking V_{TE} out of the model, mask leak was significant with p<0.001, Hazard Ratio 0.89 (0.86 to 0.93) per 10% increase.
§Ventilation frequency was not significant with p=0.63 in the univariate and p=0.18 in the multivariate Cox model and was omitted from the final models.

Table 4 Comparison of groups by time to threshold ECO_2 >2%

	Category of time to ECO_2 >2%			Kruskal-Wallis test *
	A: ECO_2 >2% in first ventilation	B: ECO_2 >2% during ventilation	C: ECO_2 >2% never achieved	P value
n	**113**	**298**	**23**	–
Expired tidal volume, V_{TE} (mL/kg)	7.3 (4.3–11.3)	4.2 (1.9–7.4)	2.9 (1.0–5.0)	<0.001*
Mask leak (%)	41 (25–60)	55 (36–43)	78 (44–93)	<0.001†
Ventilation frequency (per minute)	45 (33–61)	48 (38–69)	64 (46–73)	0.009‡
Peak inflation pressure (mbar)	35 (31–39)	36 (31–39)	33 (25–38)	0.16
Minute volume (mL/kg per minute)	325 (171–553)	201 (82–421)	154 (51–406)	<0.001§
Birth weight (kg)	3.2 (2.9–3.5)	3.1 (2.7–3.4)	2.9 (2.6–3.2)	<0.001¶
First detected heart rate (bpm)	70 (59–94)	67 (56–85)	77 (59–83)	0.15
Apgar 1 min	7 (6–7)	6 (5–7)	5 (5–7)	<0.001**
Apgar 5 min	10 (8–10)	10 (8–10)	9 (7–10)	0.19
Time from first to last ventilation (s)	126 (63–258)	217 (95–458)	66 (22–130)	<0.001††

All values are medians (IQR). For ventilation factors, we used median per group of medians per newborn within the first 30 s of ventilation. Kruskal-Wallis test was performed to rank medians. The column shows p values for comparison of all three groups, p values for significant differences between groups compared in pairs are given as footnotes.
*V_{TE}: A≠B (p<0.001), A≠C (p<0.001), B≠C (p=0.07).
†Mask leak: A≠B (p<0.001), A≠C (p<0.001), B≠C (p=0.04).
‡Ventilation frequency: A≠B (p=0.02), A≠C (p=0.008), B≠C (p=0.07).
§Minute volume: A≠C (p=0.009), B≠C (p<0.001).
¶Birth weight: A≠B (p<0.001), A≠C (p=0.010).
**Apgar at 1 min: A≠B (p<0.001), A≠C (p=0.017).
††Time from first to last ventilation: A≠B (p=0.023), A≠C (p<0.001), B≠C (p>0.001).

table S2). Substituting 5 min Apgar scores with 1 min scores did not affect the main conclusions.

Other analyses

Table 4 groups included newborns in three: (A) ECO_2 >2% at onset of BMV, (B) reached ECO_2 >2% during BMV and (C) never reached ECO_2 >2%. Group A had significantly higher BW, Apgar scores and V_{TE} and lower mask leak and ventilation rate in the first 30 s of ventilations compared with groups B and C. We found no significant differences in the clinical parameters between group B and C. However, infants in group C were ventilated with higher frequencies, had more mask leak and had lower V_{TE} in the first 30 s of BMV.

DISCUSSION

In this large observational study, ventilation factors were stronger predictors for ECO_2 than clinical markers of asphyxia during initial resuscitation of term and near-term newborns. V_{TE} >10 mL/kg, low mask leak and a ventilation frequency around 30/min were associated with the highest ECO_2.

Simultaneous collection of ventilation parameters and observation of clinical factors in a large sample of newborns allowed for analyses considering both clinical differences and quality of delivered ventilations. The main findings were replicated in alternative statistical models. The major burden of death and morbidity due to neonatal asphyxia occurs in low-income countries.[29] Even if the midwives' ventilation skills may not be representative for all places, the physiological factors affecting ventilation parameters and ECO_2 must be expected to be similar for newborns all over the world. High baseline morbidity is more likely to strengthen than hide associations with clinical factors. We do not find obvious reasons limiting the validity of the main findings in a global context.

As in any observational study, our results may be affected by unmeasured or residual confounding. It is likely that subtle interactions occurred between clinical and ventilation factors due to variations in lung compliance and muscle tone. The first detected HR defined as 'initial HR' was collected with variable delay after birth depending on when the HR sensor was applied. Apgar scores are subjective measures, and interobserver variability large.[26 30] Measures of umbilical artery pH, base excess or lactate are more objective to assess degree of asphyxia, but were not available at the study site.

We propose that ventilation characteristics associated with higher and a faster increase in ECO_2 during initial BMV are favourable to quickly establish effective gas exchange. The observed close association between V_{TE} and ECO_2 supports studies pointing to ECO_2 as an indicator of lung aeration immediately after birth.[5 6] An increase in ECO_2 with increasing minute volumes, different from later in life, further strengthens the theory that ECO_2 is diffusion limited during initial ventilation of fluid-filled newborn lungs.[31] As we observed an increase in ECO_2 for V_{TE} 10–20 mL/kg, and shorter time to reach ECO_2 >2% up to 14 mL/kg, we speculate that higher V_{TE} than the commonly recommended 4–8 mL/kg may promote a faster lung aeration. Two other studies from our group found a positive relationship between delivered V_{TE} and HR, with the most rapid increase in HR during BMV at volumes around 10 mL/kg.[4 17] Larger V_{TE} may be needed during BMV than in intubated patients to compensate for upper airway distension.[32]

We found that ventilation frequency was negatively associated with ECO_2, suggesting less effective lung aeration at high frequencies. Highest observed ECO_2 at ventilation frequencies around 30/min points to inflation rates in the lower range of recommended values as potentially more favourable, as suggested by the European resuscitation guidelines.[19 20]

Several authors have proposed that capnography may serve as feedback to identify airway obstruction during newborn resuscitation.[10 13 33] Our findings partly support this. Low ECO_2 associated with high PIP may be due to obstructed airway or low lung compliance. Mask leak and PIP effects were substantially reduced in our models when adjusting for V_{TE}, likely because they mainly worked through V_{TE} modifications. We do not see obvious ways to discriminate between airway obstruction and liquid-filled lungs as explanation for low ECO_2 before higher levels have been observed.[34] Stronger positive linear association between PIP and ECO_2 in the first ventilation sequence compared with later sequences supports a need for higher opening pressure during initial inflations.[35]

We observed a fast ECO_2 increase in the first minute of ventilation. This is line with previous studies indicating a gradual lung aeration.[7–9] Efforts to improve ventilation, like clearing the airway and reducing mask leak, probably contributed to ECO_2 increase over time. Reduced ECO_2 after ventilation pauses suggests re-entry of lung liquid and supports a recommendation for continuous, effective ventilation to non-breathing newborns.[18]

The process of lung aeration has been found to be slower during BMV than in spontaneously breathing newborns.[8 9 36 37] Newborns with gasping or spontaneous breaths before initiation of BMV have already started the lung-aeration process. This may explain higher initial ECO_2 in newborns with higher Apgar scores. Moreover, larger newborns may have higher respiratory drive and better reserves to handle complications during labour despite low initial HR and low Apgar scores, explaining the positive association between ECO_2 and BW.

Significant but weak negative associations found between Apgar scores, initial HR and ECO_2 underline that severely compromised circulation may cause persistently low ECO_2.[16 28] Waste of valuable time trying to improve correctly performed ventilations based on ECO_2 feedback may be a pitfall. To measure V_{TE} in combination with ECO_2 may reduce this risk.[36 38]

Our findings indicate that somewhat higher V_{TE} than currently recommended and a low ventilation frequency may be favourable during bag-mask ventilation of term and near-term infants at birth. However, this is an observational study and long-term outcomes have not been studied. Near-term newborns have more mature and less vulnerable lungs than premature infants, and asphyxia is often the cause when they do not start breathing spontaneously.[39] Still, the optimal V_{TE} needed to balance fast establishment of adequate ventilation to avoid brain damage against the risk for lung injury remains unclear.[6 40] Our findings alone are not sufficiently strong to change guideline recommendations, but may provide background information for future randomised studies of V_{TE}, ventilation frequency and the use of ECO_2 feedback during newborn resuscitation.

CONCLUSIONS

Ventilation factors are important predictors for ECO_2 during the first minutes of bag-mask ventilation in newborn resuscitation. V_{TE} of 10–14 mL/kg and ventilation frequency around 30/min are associated with the highest ECO_2 and the shortest time to reach ECO_2 >2%. Low ECO_2 may be useful to detect inefficient ventilation. Low BW, HR and Apgar scores are also associated with low ECO_2, and this must be accounted for in the interpretation.

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