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Clinical paper

Expired carbon dioxide during newborn resuscitation as predictor of outcome



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Abstract

Aim: To explore and compare expired CO₂ (ECO₂) and heart rate (HR), during newborn resuscitation with bag-mask ventilation, as predictors of 24-h outcome.

Methods: Observational study from March 2013 to June 2017 in a rural Tanzanian hospital. Side-stream measures of ECO₂, ventilation parameters, HR, clinical information, and 24-h outcome were recorded in live born bag-mask ventilated newborns with initial HR < 120 bpm. We analysed the data using logistic regression models and compared areas under the receiver operating curves (AUC) for ECO₂ and HR within three selected time intervals after onset of ventilation (0–30 s, 30.1–60 s and 60.1–300 s).

Results: Among 434 included newborns (median birth weight 3100 g), 378 were alive at 24 h, 56 had died. Both ECO₂ and HR were independently significant predictors of 24-h outcome, with no differences in AUCs. In the first 60 s of ventilation, ECO₂ added extra predictive information compared to HR alone. After 60 s, ECO₂ lost significance when adjusted for HR. In 70% of newborns with initial ECO₂ < 2% and HR < 100 bpm, ECO₂ reached ≥ 2% before HR ≥ 100 bpm. Survival at 24 h was reduced by 17% per minute before ECO₂ reached ≥ 2% and 44% per minute before HR reached ≥ 100 bpm.

Conclusions: Higher levels and a faster rise in ECO₂ and HR during newborn resuscitation were independently associated with improved survival compared to persisting low values. ECO₂ increased before HR and may serve as an earlier predictor of survival.

Keywords: Newborn resuscitation, Bag-mask ventilation, Expired carbon dioxide, Heart rate, 24 Hour outcome

Abbreviations: AUC, area under the receiver operating curves; BMV, bag-mask ventilation; BW, birth weight; bpm, beats per minute; ECO₂, expired carbon dioxide; GA, gestational age; HR, heart rate; Mbar, millibar; ROC, receiver operating characteristics; V_{TE}, expired tidal volume.

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Introduction

Adequate ventilation is the key to successful resuscitation in newborns who fail to initiate spontaneous breathing at birth. An increase in heart rate (HR) is currently considered the most important indicator for a positive response to ventilations. HR response is, however, an indirect measure dependent on sufficient oxygen delivery to the heart, and gives no direct feedback on lung aeration and airway patency. The 2015 international consensus for newborn resuscitation mentioned expired carbon dioxide (ECO_2) as a potentially more sensitive marker of effective ventilation, and stated that more research is needed to determine whether ECO_2 monitoring is useful to assess response to resuscitation.¹

At birth a successful transition from placental to pulmonary gas exchange is critical for survival.² ECO_2 may serve as a marker for lung aeration and pulmonary circulation.^{3,4} ECO_2 also depends on ventilation technique, and is used by resuscitation teams to aid recognizing airway obstruction, mask leak and correct endotracheal tube placement.^{5–9} In cardiopulmonary resuscitation after the newborn period, persisting low ECO_2 is associated with decreased survival.^{10–12} Results from clinical studies in mainly preterm newborns suggest that ECO_2 increases before HR during positive pressure ventilation in the delivery room.^{3,13,14} Linde et al. found that median ECO_2 in the first minute of bag-mask ventilation (BMV) at birth was lower in newborns who died before 24 h of age compared to survivors.¹⁵

The aims of this study were to explore ECO_2 as a predictor of 24-h outcome (survival vs death) during newborn resuscitation with BMV, and to compare the predictive information of ECO_2 and HR.

Methods

Study design and setting

This descriptive observational study is part of Safer Births, a research project on labour surveillance and newborn resuscitation in low-income settings.¹⁶ We used data collected between March 1st 2013 and June 1st 2017 at Haydom Lutheran Hospital, a rural Tanzanian referral hospital with 3600–4600 deliveries annually.¹⁷

The local procedure for newborn resuscitation followed Helping Babies Breathe (HBB) emphasizing stimulation and early initiation of BMV, excluding chest compressions, intubation and medication.¹⁸ Newborn resuscitation was mainly the responsibility of midwives. Cord clamping was done prior to BMV. After resuscitation the midwives decided, based on the clinical condition, whether to keep the newborn with the mother or transfer to a neonatal ward offering basic care including antibiotics, phototherapy, and intravenous fluids, but no respiratory support except supplemental oxygen by nasal cannula.¹⁹

Data collection

A newborn resuscitation monitor (Laerdal Global Health, Stavanger, Norway) was mounted on the wall above all resuscitation tables.²⁰ 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 measures of ECO_2 (ISA™, Masimo, Irvine, California, USA), pressure (Freescale semiconductor,

Austin, Texas, USA) and flow (Acutronic Medical Systems, Hirzel, Switzerland) were placed between the mask and bag. The monitors started data recording automatically when used, and provided HR feedback during resuscitation. ECO_2 and ventilation parameters were not displayed. Pulse oximetry was not available. Trained non-medical research assistants observed all deliveries documenting perinatal information, time intervals, and 24-h outcomes.

We included all live-born newborns with initial HR < 120 beats per minute (bpm) and available data for both ECO_2 and HR ($n = 434$) (Fig. 1). Stillborns, defined locally as Apgar score 0 at both 1 and 5 min or gestational age (GA) < 28 weeks, were excluded. We also excluded newborns ventilated with positive end-expiratory pressure as part of a concurrent randomized trial as this could potentially affect ECO_2 and HR.²¹ Data from the same cohort of newborns were used in a recently published article on predictors of ECO_2 during newborn resuscitation.²²

Regression models

To study the associations between 24-h outcome (survival vs. death) and the covariates ECO_2 , HR, and expired tidal volume (V_{TE}), we performed logistic regression analyses. In the main models, ECO_2 and HR were studied independently (unadjusted). In secondary models, ECO_2 and HR were mutually adjusted, and then adjusted for V_{TE} . ECO_2 was recorded as maximum percent of expired air per ventilation. All observations of ECO_2 , regardless of leak and V_{TE} , were included. HR was smoothed per approximately 12 beats per algorithm in the monitor.

Exploring graphs made to display ECO_2 and HR by time in the first 300 s of ventilation (Supplemental Fig. 1), we selected three time intervals (0–30 s, 30.1–60 s, and 60.1–300 s) for further analyses. Due to large variations in especially ECO_2 (between ventilations), we decided to study both the single maximum value and the median of all recorded ECO_2 - and HR-values per newborn within each time interval. We also studied time from first delivered ventilation until ECO_2 reached $\geq 2\%$ and HR ≥ 100 bpm in secondary models. To determine time to $\text{ECO}_2 \geq 2\%$, we used ECO_2 smoothed as means per 5

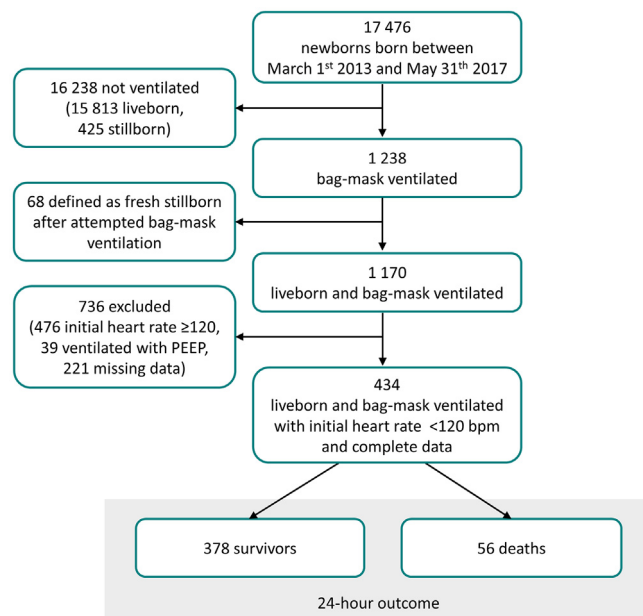


Fig. 1 – Flow chart.

ventilations. For V_{TE} , the median value per newborn within each time interval was used.

Non-linear associations between ECO_2 , HR and 24-h outcome were assessed by categorical logistic regression models. Due to potential differences in pathophysiology between preterm or small for GA newborns compared to term newborns, stratified analyses for birth weight (BW) ≥ 2500 g vs. < 2500 g were performed.

Further analyses

Receiver operating characteristics (ROC) curves graphically display sensitivity as a function of 1-specificity for all possible cut off values of the test parameters in diagnostic tests with binary outcomes.²³ The area under the ROC curves (AUC) gives a measure for the total predictive information of the test parameters. To estimate the classification accuracy of ECO_2 and HR as predictors of 24-h survival, we made ROC curves and calculated AUC for predicted sensitivity and specificity of the covariates, based on the results of the main (unadjusted) logistic regression models. We used Pearson Chi Square tests to compare the AUCs for maximum ECO_2 and HR within each time interval. We further plotted sensitivity and specificity for selected cut-off values for maximum ECO_2 ($\geq 1, 2$ and 4%) and HR ($\geq 60, 100$ and 120 bpm) in the ROCs. We also calculated AUCs for the secondary (adjusted) models to estimate the total predictive information of all included covariates.

The ECO_2 and HR thresholds of 2% and 100 bpm, respectively, were studied in more detail. Among newborns with initial $ECO_2 < 2\%$ and HR < 100 bpm, we compared time intervals from first ventilation until $ECO_2 \geq 2\%$ and HR ≥ 100 bpm. We performed post hoc analyses using Wilcoxon rank sum tests to assess for differences in initial HR, Apgar scores, BW and ventilation factors (V_{TE} and mask leak) depending on which threshold was reached first.

Data processing and analyses were performed using Matlab (MathWorks, Natick, MA, USA) and Stata SE version 16 (StataCorp., Texas, USA). Significance level was set to $p < 0.05$.

Ethical considerations

Ethical approval was granted by the National Institute for Medical Research in Tanzania (Ref. NIMR/HQ/R.8a/Vol.IX/1434) and the

Regional Committee for Medical and Health Research Ethics for Western Norway (Ref.2013/110). All women were informed. Consent was not considered necessary by the ethical committees.

Results

Among 434 live born newborns who received BMV, with first registered HR < 120 bpm and complete data, 378 survived to 24 h, 56 (12.9%) died (Fig. 1). Survivors had significantly higher BW and Apgar scores than deaths and were ventilated for a shorter time (Table 1).

ECO_2 and HR as predictors for survival

Both ECO_2 and HR increased during BMV, with higher levels in survivors compared to deaths (Fig. 2 and Supplemental Fig. 1). Odds ratios for 24-h survival increased significantly with higher levels of ECO_2 and HR (Table 2). In the first minute of BMV, maximum ECO_2 and HR were both significant predictors for survival in adjusted models, indicating independent effects. After the first minute, ECO_2 lost significance when adjusted for HR. Adjusting for V_{TE} non-significantly increased the odds ratios for survival by ECO_2 .

When studied independently, we found no significant differences in AUCs for maximum ECO_2 compared to HR (Fig. 3). Though not significant, maximum ECO_2 gave slightly larger AUCs within the first minute of BMV. After the first minute, AUC for HR was largest. AUCs were similar using medians compared to maximums per time interval for both ECO_2 and HR (Table 2).

Sensitivity and specificity for selected cut-offs of maximum ECO_2 and HR within time intervals are plotted in ROC curves in Fig. 3. Reaching $ECO_2 \geq 2\%$ within the first 30 s of ventilation had a higher sensitivity to predict 24-h survival than HR ≥ 100 bpm (80% versus 68%). After one minute of ventilation, $ECO_2 \geq 2\%$ had slightly lower sensitivity than HR ≥ 100 bpm (94% versus 99%).

In categorical models, we found no non-linear associations to support decreased survival with high levels of ECO_2 or HR (Supplemental Table 1). The predictive information of ECO_2 and HR on survival were weaker in newborns with BW $<$ compared to ≥ 2500 g (Supplemental Table 2).

Table 1 – Comparison of demographic and delivery room data between survivors and deaths at 24 h.

	Survivors		Deaths		p-value
	n		n		
Birth weight (grams)	378	3100 (2780, 3450)	56	3000 (2500, 3200)	0.01
Birth weight < 2500 g, n = 60 (14%)	46	12%	14	25%	0.01
Gestational age (weeks)	356	38 (37, 40)	47	38 (36, 39)	0.46
Gestational age < 37 weeks, n = 97 (22%)	85	21%	12	22%	0.86
Female, n = 169 (39%)	146	41%	23	39%	0.73
Caesarean Section, n = 215 (50%)	182	59%	33	48%	0.13
Time from birth to cord clamping (seconds)	376	22 (12, 57)	55	18 (13, 49)	0.37
Apgar at 1 min	378	7 (5, 7)	56	4 (3, 5)	<0.001
Apgar at 5 min	378	10 (8, 10)	56	7 (4, 10)	<0.001
Time from birth to first BMV (seconds)	375	125 (84, 160)	54	111 (77, 158)	0.49
Time from first to last BMV (seconds)	378	162 (71, 317)	56	624 (227, 1358)	<0.001

Data are displayed as medians (IQR) or numbers (%). P-values were calculated by Wilcoxon's rank sum test or Pearson's Chi² test as appropriate. HR = heart rate, BMV = bag-mask ventilation.

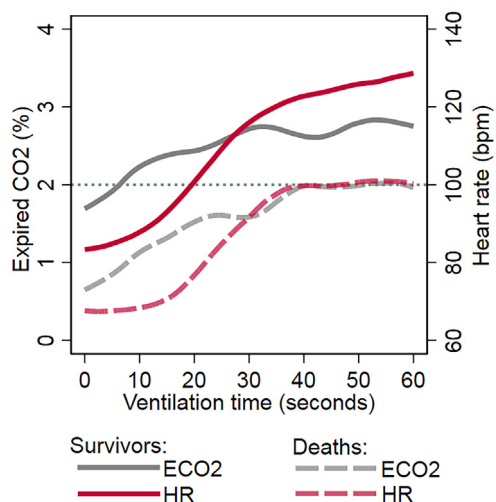


Fig. 2 – ECO_2 and HR by time in survivors compared to deaths in the first 60 s of bag-mask ventilation.

ECO_2 increased before HR in a majority of newborns, survivors had higher levels of ECO_2 and HR than deaths. The graphs are smoothed local polynomial plots of all measured values for ECO_2 and HR in all included newborns.

ECO_2 = expired CO_2 , HR = heart rate.

Time to thresholds

The time to reach $\text{ECO}_2 \geq 2\%$ and $\text{HR} \geq 100$ bpm, in analyses including only newborns with initial measures below the thresholds, was significantly lower in survivors compared to deaths (Table 3). Odds ratio (95% CI) for survival per minute increase in time to reach $\text{ECO}_2 \geq 2\%$ was 0.83 (0.71, 0.97) compared to 0.56 (0.40, 0.78) per minute before HR reached ≥ 100 bpm. Thus, 24-h survival was reduced by approximately 17% per minute before ECO_2 reached $\geq 2\%$ and 44% per minute before HR reached ≥ 100 bpm.

A majority of newborns (159/226, 70%) who reached both thresholds, crossed $\text{ECO}_2 \geq 2\%$ before $\text{HR} \geq 100$ bpm. This was evenly distributed between the groups (131/188 (70%) survivors compared to 28/38 (74%) deaths, $p = 0.62$). Newborns who reached $\text{HR} \geq 100$ bpm first had lower median V_{TE} (3.9 (1.0–8.2) vs. 5.6 (2.9–10.1) ml/kg, $p = 0.007$) and a higher leak (64 (35–83) vs. 45 (22–71)%, $p = 0.005$) in ventilations prior to reaching the threshold compared to newborns who reached $\text{ECO}_2 \geq 2\%$ first. Time to reach $\text{HR} \geq 100$ bpm was independent of which threshold was reached first (31 (21–61) s), but time to reach $\text{ECO}_2 \geq 2\%$ was significantly longer in newborns who crossed $\text{HR} \geq 100$ bpm first (12 (5–29) vs. 67 (39–120) s, $p < 0.001$). We found no differences in initial HR, Apgar score or BW depending on which threshold was reached first.

Discussion

Association between HR and outcome in newborn resuscitation is well established, and a cornerstone for recommendations to ventilate if HR is < 100 bpm.^{15,19,24–27} New in this study is that ECO_2 measured during BMV at birth can also serve as a predictor of survival. We found ECO_2 to be an earlier marker of 24-h survival than HR. After the first

minute of ventilation, ECO_2 added no extra predictive information compared to HR.

The main finding of higher levels of ECO_2 as a predictor of survival is similar to results from cardiopulmonary resuscitation after the newborn period.^{11,12} However, newborns in need of positive pressure ventilation at birth are rarely in cardiac arrest. In a recent study of apnoeic newborns, the first recorded HR was distributed in two peaks around 60 and 165 bpm.²⁵ Thus, an increase in ECO_2 during newborn resuscitation, is usually not a sign of return of spontaneous circulation, but may be seen as a marker for established pulmonary gas exchange.

Measured values of ECO_2 during mask ventilation will generally be lower than in intubated newborns due to dilution in a larger dead space and occurrence of leak and obstructed airway. No exclusions can be done when interpreting measured values during ongoing resuscitation, and the ventilation technique is potentially relevant for survival. We therefore decided to retain all observations. This may explain the large variation in ECO_2 between ventilations, and a lower median ECO_2 in our results than in studies where exclusions of ventilations with low V_{TE} or high leak were done.^{3,4,28,29}

As ECO_2 during BMV is highly dependent on ventilation parameters, especially V_{TE} ,^{6,22} inadequate ventilation cannot be ruled out as a contributing explanation for low ECO_2 in non-surviving newborns. However, we propose that the reason for lower ECO_2 in deaths compared to survivors was mainly a more severely compromised clinical condition at birth. Prior studies from the same study site have estimated that around 60% of 24-h newborn deaths were due to intrapartum related events (birth asphyxia and meconium aspiration syndrome).^{30,31} Despite a presumptive larger impact of ventilation technique on medians compared to maximums, we found maximum ECO_2 within the selected time interval to predict survival as good as medians. If newborn death was often associated with inadequate V_{TE} , we would expect adjustment for V_{TE} to reduce OR and AUC in models with ECO_2 . However, adjusting for V_{TE} in our analyses non-significantly increased the predictive information, especially of median ECO_2 . This suggests against inadequate ventilation as a major cause of death, but rather points to low ECO_2 with simultaneously high V_{TE} as a sign of a more compromised clinical condition.

Three prior smaller studies of mainly preterm newborns in high resourced settings have shown a significant increase in ECO_2 preceding HR response during mask ventilation in newborn resuscitation.^{3,13,14} Different from these studies, our study was performed in a larger sample of mainly term newborns in rural Tanzania. In concordance with the previous studies, we found that among newborns who reached both predefined thresholds, 70% crossed $\text{ECO}_2 \geq 2\%$ before $\text{HR} \geq 100$ bpm. This underpins ECO_2 as an earlier marker for treatment response than HR. We also found a group who reached $\text{HR} \geq 100$ bpm before $\text{ECO}_2 \geq 2\%$. A lower V_{TE} and higher leak in this group, suggest suboptimal ventilations as explanation for the slower rise in ECO_2 . Because there were no differences in time to $\text{HR} \geq 100$ bpm for those who reached $\text{HR} \geq 100$ bpm first compared to those who reached $\text{ECO}_2 \geq 2\%$ first, we speculate that these newborns were likely less severely asphyxiated, despite the low initial HR, and may have had some spontaneous breathing and intact reflexes. The delay from birth until BMV was started may have contributed to increased differences in ECO_2 and HR between mild and severely compromised newborns.

Slight differences in predictive value of ECO_2 and HR in newborns with BW < 2500 g compared to ≥ 2500 g, may be due to a higher risk of

Table 2 – Logistic regression models and area under receiver operating characteristics curves (AUC) for 24-h survival by maximum (upper panel) and median (lower panel) expired CO₂ and heart rate per newborn for the three selected time intervals.

		Main models		Secondary models				
		Unadjusted		Mutual adjustment ECO ₂ /HR		Adjusted for ECO ₂ /HR and V _{TE} ^a		
Maximum ECO ₂ and HR		n	OR (95% CI)	AUC ^b	OR (95% CI)	AUC ^c	OR (95% CI)	AUC ^c
0–30 s of BMV		422						
ECO ₂	Per 1 pp increase		1.31 (1.17, 1.46) ^d	0.72	1.24 (1.10, 1.39) ^d	0.73	1.27 (1.12, 1.44) ^d	0.74
HR	Per 10 bpm increase		1.18 (1.09, 1.28) ^d	0.67	1.10 (1.00, 1.20) ^f		1.10 (1.00, 1.20) ^f	
30.1–60 s of BMV		363						
ECO ₂	Per 1 pp increase		1.26 (1.13, 1.40) ^d	0.69	1.17 (1.04, 1.32) ^e	0.69	1.18 (1.02, 1.22) ^f	0.69
HR	Per 10 bpm increase		1.18 (1.09, 1.28) ^d	0.66	1.11 (1.02, 1.22) ^f		1.12 (1.02, 1.22) ^e	
60.1–300 s of BMV		354						
ECO ₂	Per 1 pp increase		1.18 (1.07, 1.32) ^e	0.62	1.06 (0.95, 1.19)	0.64	1.07 (0.95, 1.20)	0.68
HR	Per 10 bpm increase		1.28 (1.17, 1.40) ^d	0.64	1.25 (1.13, 1.38) ^d		1.27 (1.14, 1.41) ^d	
Median ECO₂ and HR								
0–30 s of BMV		422						
ECO ₂	Per 1 pp increase		1.43 (1.17, 1.74) ^d	0.65	1.31 (1.08, 1.60) ^e	0.71	1.46 (1.16, 1.83) ^d	0.74
HR	Per 10 bpm increase		1.28 (1.13, 1.45) ^d	0.68	1.23 (1.09, 1.40) ^d		1.22 (1.07, 1.38) ^e	
30.1–60 s of BMV		363						
ECO ₂	Per 1 pp increase		1.27 (1.08, 1.49) ^e	0.65	1.15 (0.97, 1.37)	0.67	1.21 (0.99, 1.47)	0.67
HR	Per 10 bpm increase		1.16 (1.07, 1.25) ^d	0.65	1.11 (1.02, 1.22) ^f		1.12 (1.02, 1.22) ^f	
60.1–300 s of BMV		354						
ECO ₂	Per 1 pp increase		1.20 (1.02, 1.40) ^f	0.61	1.00 (0.84, 1.21)	0.63	1.07 (0.88, 1.29)	0.67
HR	Per 10 bpm increase		1.20 (1.11, 1.29) ^d	0.63	1.19 (1.09, 1.31) ^d		1.20 (1.09, 1.32) ^d	

ECO₂ = expired CO₂, HR = heart rate, OR = Odds Ratio, pp = percent point, bpm = beats per minute, V_{TE} = expired volume, BMV = bag-mask ventilation, AUC = area under the receiver operator curve.

The main models present unadjusted OR of 24-h survival for both ECO₂ and HR independently. The secondary models present OR of 24-h survival for 1) ECO₂ and HR when mutually adjusted and 2) ECO₂ and HR when adjusted for each other and for the median V_{TE} within each time interval. The AUC values displayed, were calculated based on the results of the corresponding logistic regression models. Newborns (n) with available data for both ECO₂ and HR within each time interval were included.

^a Median V_{TE} turned significant with negative impact on survival ≤30 s and between 60.1–300 s of ventilation in models with median ECO₂ and between 60.1–300 s in models with HR. Median V_{TE} was not associated with survival in unadjusted models.

^b Receiver operating characteristics curves and AUC with 95% confidence intervals for maximum ECO₂ and HR in the unadjusted models, and statistical tests to assess for differences, are displayed in Fig. 3.

^c AUC reported for adjusted models describes the combined predictive information of all the included parameters in the model.

^d p < 0.001.

^e p < 0.01.

^f p < 0.05.

death by other causes than birth asphyxia in newborns who were preterm or small for GA.³⁰

To our knowledge, this is the first study to compare ECO₂ and HR measured in the delivery room as predictors of 24-h survival in newborns who receive BMV at birth. The unique research infrastructure comprising both continuous prospective observer-monitored and automatically recorded biomedical signal-data of a large cohort of newborns is a major strength. Data were collected in a rural low-income setting with high morbidity, long transport and potential delay for complicated deliveries to be assisted, representative for where most newborn deaths occur.³² The local resuscitation procedure followed HBB.¹⁸ Advanced neonatal care and respiratory support after initial resuscitation, including continuous positive airway pressure therapy, were not available. This likely affected 24-h survival, and thus the results may not be generalizable to all settings. Variation in clinical condition between included newborns and experience between providers will naturally occur in all studies performed in real life situations. This make the results more representative for newborns in need for respiratory support at birth,

but is also a limitation as some newborns may have had some spontaneous breathing and some may have received suboptimal care.

Large breath-to-breath variation makes ECO₂ measured during BMV potentially difficult to interpret in clinical situations. Finding maximum ECO₂ to give as good predictive information as median values, we suggest using the highest observed values within time intervals if ECO₂ should be utilised as prognostic information during newborn resuscitation.

Plotting selected cut-off values for maximum ECO₂ and HR in ROC curves, we found that choosing lower cut-offs would give a more sensitive, but less specific predictive test for survival than higher cut-off values. ECO₂ ≥2% is approximately equivalent to a partial pressure of 15 mmHg or 2 kPa, which is the limit for colour change in colorimetric ECO₂-sensors.¹⁴ This may be a reasonable choice to indicate successful lung aeration and favourable prognosis during BMV of asphyxiated newborns.

The dual nature of ECO₂ as both a marker for severity of the clinical condition and of ventilation quality,²² makes ECO₂-monitoring

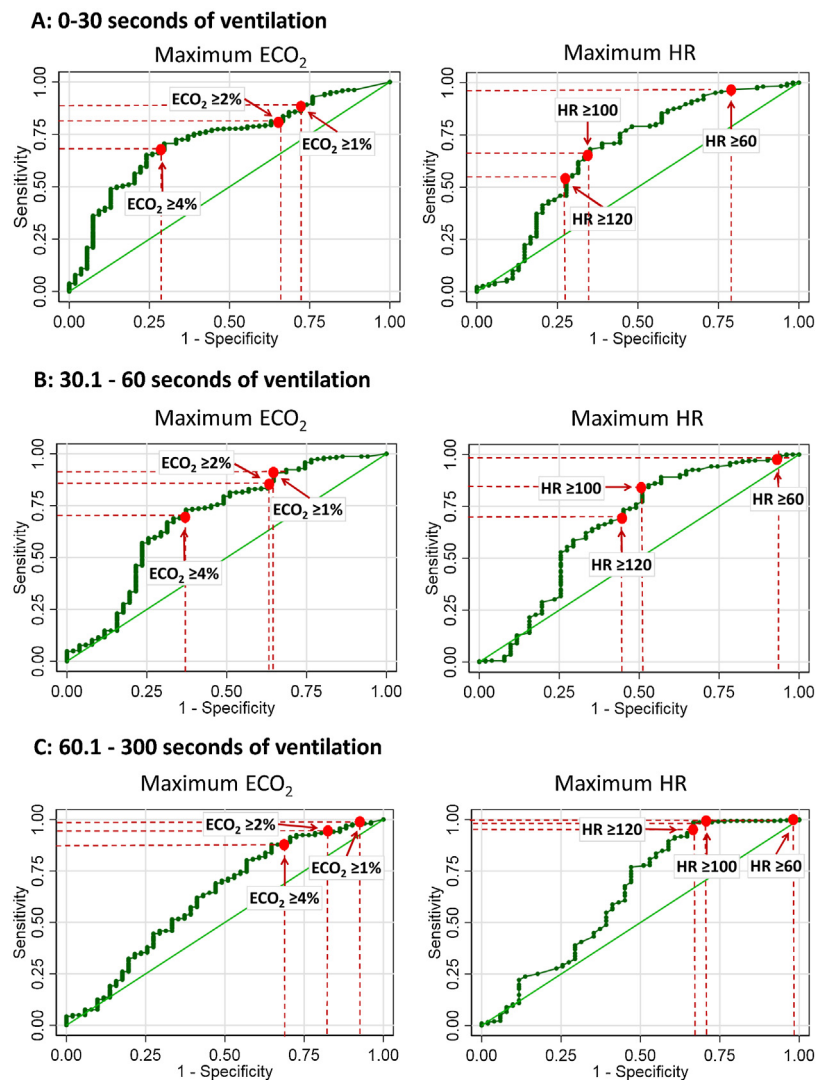


Fig. 3 – Receiver operating characteristics curves for maximum ECO_2 and HR within time intervals as predictors for 24-h survival.

The graphs display ROC curves for maximum ECO_2 and HR within the three selected time intervals after start of ventilation (A: 0–30 s, B: 30.1–60 s, and C: 60.1–300 s) as predictors for 24-h survival. Sensitivity and specificity for selected cut-off values of maximum ECO_2 (left panel; $\text{ECO}_2 \geq 1, 2, \text{ and } 4\%$) and HR (right panel; $\text{HR} \geq 60, 100, \text{ and } 120$ bpm) are plotted.

Comparison of AUC for ECO_2 and HR (Pearsons Chi^2 -test).

A: AUC for maximum $\text{ECO}_2 = 0.72$ (0.65, 0.79), AUC for maximum HR = 0.67 (0.58, 0.76), $p = 0.21$.

B: AUC for maximum $\text{ECO}_2 = 0.69$ (0.60, 0.78), AUC for maximum HR = 0.66 (0.56, 0.76), $p = 0.56$.

C: AUC for maximum $\text{ECO}_2 = 0.62$ (0.53, 0.71), AUC for maximum HR = 0.64 (0.54, 0.64), $p = 0.74$.

ECO_2 = expired CO_2 in percent of expired air, HR = heart rate in beats per minute, ROC = Receiver Operating Characteristics, AUC = area under the ROC curves.

potentially useful during resuscitation for prognostic information and to help improve ventilations. However, the duality also implies pitfalls for the interpretation. Providers must be aware that low ECO_2 may have several causes, including high leak, airway obstruction, unaerated lungs or compromised pulmonary circulation.^{3,4,6,22} The results of this study indicate that persisting low ECO_2 may, like persisting low HR, be used to support decisions to discontinue resuscitation. $\text{ECO}_2 \geq 2\%$ or $\text{HR} \geq 100$ should encourage further efforts, even in seemingly non-viable newborns. However, we found low specificities of ECO_2 or HR used as tests to predict survival, and strongly advice against

depending on this alone. The information must be combined with thorough considerations taking the quality of given ventilations, clinical responses, duration of resuscitation and availability of advanced neonatal care into account.

Importantly, HR was the only displayed parameter in this study, and thus the midwives could not adjust ventilation technique as a response to changes in ECO_2 . A feedback on ECO_2 may help providers improve ventilation technique, which may further improve prognosis and the predictive information by ECO_2 . We do not think that ECO_2 should replace HR for prognostic information during newborn

Table 3 – Comparison of time to expired CO₂ ≥2% and heart rate ≥100 bpm between survivors and deaths at 24 h.

	Survivors	Deaths	p-value
Expired CO₂ (ECO₂)			
Time from first BMV until ECO ₂ ≥2% (seconds) ^a	16 (6, 47)	37 (11, 93)	0.06 ^d
Time from birth until ECO ₂ ≥2% (seconds) ^b	137 (95, 197)	149 (119, 280)	0.12 ^d
Number of newborns with ECO ₂ ≥2% in first BMV	109 (29%)	4 (7%)	0.001 ^e
Number of newborns who did not reach ECO ₂ ≥2% while monitored ^c	15 (4%)	8 (14%)	0.001 ^e
Heart rate (HR)			
Time from first BMV until HR ≥ 100 bpm ^a	27 (19, 50)	47 (24, 127)	<0.001 ^d
Time from birth until HR ≥ 100 bpm ^b	151 (110, 209)	185 (125, 274)	0.02 ^d
Number of newborns with HR ≥ 100 bpm at start of BMV	108 (29%)	4 (7%)	0.001 ^e
Number of newborns who did not reach HR ≥ 100 bpm while monitored ^c	4 (1%)	8 (14%)	<0.001 ^e

^a Newborns with ECO₂ <2% (254 survivors and 44 deaths) or HR < 100 bpm (266 survivors and 44 deaths) at or after start of BMV were included.

^b The times given are based on available data. ECO₂-data was not available before initiation of BMV, HR-data depended on placement of the HR-sensor around the newborn's trunk. ECO₂>2% and/or HR > 100 bpm may have occurred between birth and initiation of BMV in some newborns.

^c The time interval with monitoring varied between newborns and could be shorter than 5 min in newborns with fast clinical improvement, and longer in newborns in need for prolonged ventilation.

^d Wilcoxon's rank sum test ECO₂ = Expired CO₂, BMV = bag-mask ventilation, HR = heart rate.

^e Pearson's Chi²-test.

resuscitation. However, being an earlier and more direct marker of effective ventilation, ECO₂ may add useful information. In low resourced settings, colorimetric end-tidal CO₂-detectors may be more easily available than HR monitoring.¹⁴ Further clinical trials with ECO₂-feedback to the provider are needed to address the practical value before ECO₂-monitoring during BMV in newborn resuscitation could be recommended for routine clinical use.

Conclusions

ECO₂ during BMV in the delivery room can predict 24-h survival. ECO₂ increased before HR in most cases. ECO₂ may serve as an early marker for severity of clinical condition, ventilation quality, treatment response and prognosis during newborn resuscitation.

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Conflicts of interest

Joar Eilevstjønn is an employee at Laerdal Medical. The other authors have no potential conflicts of interest to disclose.

CRedit authorship contribution statement

Holte designed the study, carried out the analyses, and drafted the initial manuscript. Erdsdal and Klingenberg contributed to study design, analysis and writing. Erdsdal also planned and supervised data collection, and is the principal investigator of the Safer Births study group. Eilevstjønn designed the equipment used for data collection, gave technical support, extracted and processed data and contributed to analysing the data. Stigum was the study statistician providing supervision and quality control of the statistical analyses. Kidanto and Jatosh coordinated and supervised data collection. Størdal conceptualized and designed the study together with the first author, and contributed considerably to data analyses and in the writing process. All authors reviewed and revised the manuscript critically, approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.resuscitation.2021.05.018>.

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