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Predictors of extubation success: a population-based study of neonates below a gestational age of 26 weeks

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ABSTRACT

Objective The aim of the study was to investigate first extubation attempts among extremely premature (EP) infants and to explore factors that may increase the quality of clinical judgement of extubation readiness.

Design and method A population-based study was conducted to explore first extubation attempts for EP infants born before a gestational age (GA) of 26 weeks in Norway between 1 January 2013 and 31 December 2018. Eligible infants were identified via the Norwegian Neonatal Network database. The primary outcome was successful extubation, defined as no reintubation within 72 hours after extubation.

Results Among 482 eligible infants, 316 first extubation attempts were identified. Overall, 173 (55%) infants were successfully extubated, whereas the first attempt failed in 143 (45%) infants. A total of 261 (83%) infants were extubated from conventional ventilation (CV), and 55 (17%) infants were extubated from high-frequency oscillatory ventilation (HFOV). In extubation from CV, pre-extubation fraction of inspired oxygen (FiO_2) ≤0.35, higher Apgar score, higher GA, female sex and higher postnatal age were important predictors of successful extubation. In extubation from HFOV, a pre-extubation FiO_2 level ≤0.35 was a relevant predictor of successful extubation.

Conclusions The correct timing of extubation in EP infants is important. In this national cohort, 55% of the first extubation attempts were successful. Our results suggest that additional emphasis on oxygen requirement, sex and general condition at birth may further increase extubation success when clinicians are about to extubate EP infants for the first time.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Identifying the optimal time for the first extubation of extremely preterm infants is complex and clinically challenging.

⇒ A large proportion of infants born before 26 weeks' gestational age are reintubated after their first extubation attempt.

WHAT THIS STUDY ADDS

⇒ This study identifies factors that predict whether extubation of extremely premature infants, clinically considered ready for extubation, will succeed in the first attempt.

⇒ Pre-extubation fraction of inspired oxygen (FiO_2) ≤0.35, higher 5 min Apgar scores, higher gestational age, female sex and higher postnatal age at extubation are associated with successful first extubation attempts.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We suggest pre-extubation FiO_2 at 0.35 as a cut-off level predictive for extubation outcome.

⇒ Inclusion of sex and general condition at birth may improve clinical judgement of extubation readiness for the most immature infants.

INTRODUCTION

Most extremely premature (EP) infants born before a gestational age (GA) of 26 weeks receive mechanical ventilation (MV).[1 2] Although MV may be life-saving, ventilator-induced lung injury increases the risk of chronic respiratory morbidity.[3 4] Therefore, clinicians strive for extubation as soon as possible. Extubation failure is common, and associated with longer duration of MV, increased length of hospital stay and increased risk of nosocomial infections and death.[5–9] Clinical assessment of the ideal timing of extubation for EP infants is complex, including identification of optimal pre-extubation, periextubation and postextubation management.[10] Consequently, studies that can help predict successful extubation in EP infants are warranted and of clinical importance.[11]

Several studies have investigated extubation readiness in premature infants.[12–14] A systematic review and meta-analysis of predictors of extubation readiness found insufficient

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evidence to support the use of any predictors over clinical judgement alone.[15] Although various prediction models have been developed, none have been widely accepted in clinical practice.[16–18] Gupta *et al* developed a prediction model for extubation success and proposed an extubation calculator for use in clinical practice.[18] A recent study conducted at two tertiary perinatal centres in Australia suggested that the extubation outcome is associated with the mean airway pressure (MAP) and GA.[19] However, these previous studies have examined populations of EP infants with a mean GA of 26–27 weeks, potentially limiting the applicability to the most immature infants. Hence, the primary aim of our study was to investigate infant characteristics and ventilation parameters at first extubation attempt in a national cohort of EP infants below 26 weeks GA, and second to explore factors that may increase the quality of clinical judgement of extubation readiness.

METHODS

We conducted an analysis of prospectively registered data from the Norwegian Neonatal Network (NNN), supplemented by data extracted from patient records, to explore the first extubation events among premature infants <26 weeks GA born in Norway between 1 January 2013 and 31 December 2018. Eligible infants were identified in the NNN database. An information letter describing the purpose of the study was distributed to the infants' mothers, including an opt-out alternative. Infants were automatically enrolled in the study if the mother did not respond to the letter within 4 weeks to decline participation.

Demographic and clinical factors with a potential predictive effect on extubation success were determined a priori by the study investigators and were based on clinical experience and prior research in the field. Data regarding MV settings and blood gas samples related to the extubation events were extracted from patients' medical records at the 10 neonatal intensive care units (NICUs) where the infants had been treated. A senior clinician at each participating NICU reported the unit's clinical extubation strategy during the study period.

Variables and definitions

The primary outcome was a successful first extubation attempt, defined as no reintubation event within 72 hours. We also explored success rates within 7 days with no reintubation. Prenatal variables included antenatal steroids, mode of delivery and plurality. Demographic variables included GA, sex, birth weight (BW) and weight for GA. Apgar score at 5 min and Clinical Risk Index for Babies (CRIB II) score were included as variables describing general condition at birth and illness severity score. Delivery room variables included endotracheal intubation and surfactant administration.

Pre-extubation variables extracted from medical records included the last registered ventilator mode prior to extubation. For infants extubated from conventional ventilation (CV), we extracted fraction of inspired oxygen (FiO_2), peak inflation pressure (PIP; set for infants receiving pressure-limited ventilation and measured for those receiving volume-targeted ventilation-VTV), MAP and the ventilator set rate. For infants extubated from high-frequency oscillatory ventilation (HFOV), FiO_2 and MAP values were extracted. For all variables, both the last registered value and mean values for the last 6 hours prior to the extubation attempt were extracted.

For all included infants, weight at extubation and blood gas variables measured a maximum of 12 hours prior to extubation were extracted. The Ventilation Index (VI) and Respiratory Severity Score (RSS) were calculated and applied as objective measures of respiratory illness. VI was calculated as partial pressure of carbon dioxide (pCO_2) in arterial, venous or capillary blood multiplied by the ventilator set rate multiplied by the difference between PIP and positive end expiratory pressure, all divided by 1000.[20] RSS was calculated as a product of MAP and FiO_2.[21] Growth throughout the MV course was calculated based on the difference between the infants' weight on the day of intubation and the day of extubation. Information regarding caffeine and postnatal corticosteroid therapy on the day of extubation was recorded. Postextubation variables included the mode of non-invasive respiratory support delivered immediately after extubation. Accidental extubation events were identified by screening of notes written by the physician and nurses in charge on the day of extubation.

Statistical analyses

Demographic data were expressed as numbers with proportions (%), means with SD, or medians with 25th and 75th percentiles (IQR). We compared the perinatal and peri-extubation characteristics of infants successfully extubated at the first attempt with those who failed. Extubations from CV and HFOV were explored separately.

Categorical variables were compared between successful and failed extubations by using the χ^2 test or Fisher's exact test when appropriate. Continuous variables were analysed using a Wilcoxon rank-sum test. The pre-extubation variables, FiO_2 and RSS were examined for cut-off points at the 95th percentiles for successfully extubated infants.

Logistic regression modelling to identify variables predicting extubation success was applied separately for the extubations from CV and HFOV. Relevant variables based on clinical significance were included in the logistic regression models. All multivariable logistic regression models were internally validated by bootstrapping, using 1000 bootstrap samples to assess overfitting and provide shrinkage factors for adjusting regression coefficients. We assessed the model performance in terms of the Nagelkerke R-squared (R^2) from logistic regression, calibration slope and area under the curve before and after internal validation with optimism corrected estimates, please

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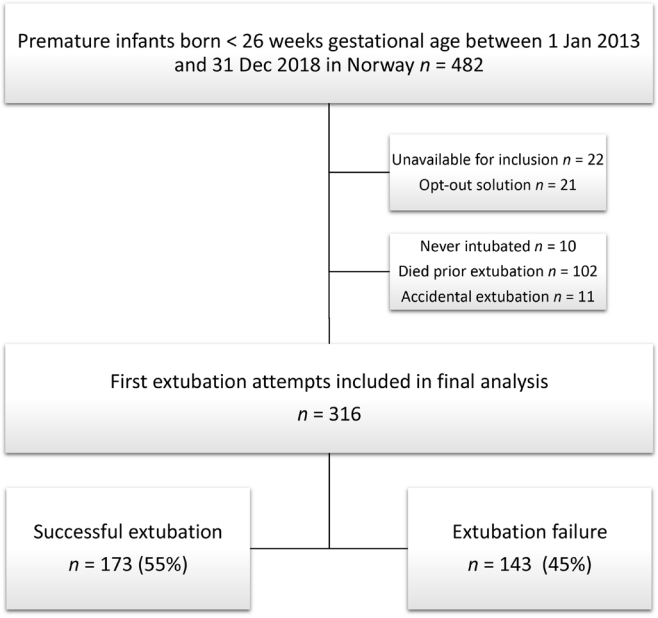

Figure 1 Flowchart of infants in the study.

see[22 23] for a through statistical explanation of internal validation with bootstrapping.

The threshold for statistical significance was set at p<0.05. Initial summary statistics and comparison tests were performed using Stata/MP V.16.1 and internal validation was conducted using the R package rms.[24]

RESULTS

During the 6-year study period, 482 EP infants of <26 weeks GA received treatment in Norwegian NICUs (figure 1). Of these, 43 (9%) infants were excluded because the mothers' address could not be verified or the mother chose to opt out. There were no statistical differences in GA, BW or mortality before discharge between infants who were included versus excluded (data not shown). Furthermore, 10 (2%) infants were excluded because they only received non-invasive respiratory support, 102 (21%) died prior to the first extubation attempt and 11 (2%) infants had an identified accidental extubation. In the final analysis, 316 infants with first extubation attempts were included, 173 (55%) were successfully extubated and 143 (45%) failed. While exploring success rates using the 7-day definition, 138 (44%) infants were successfully extubated.

Clinical extubation criteria and ventilator mode at extubation

Similar extubation criteria were reported in all participating units. Infants treated with CV were generally considered ready for extubation with a sufficient respiratory drive, PIP <20 cm H_2O and FiO_2 <0.3–0.4. Two NICUs reported clinical considerations for extubation readiness in infants treated with HFOV, that is, MAP at 7–8 cm H_2O and a FiO_2 requirement <0.3–0.4.

Overall, a total of 261 (83%) and 55 (17%) infants were extubated from the CV and HFOV, respectively.

Characteristics at birth

Characteristics at birth in infants with successful and failed first extubation attempts are presented in table 1. Antenatal steroids were given to 298 (94%) infants, and 183 (61%) infants received a complete course. There was no association between receiving antenatal steroids and extubation outcomes.

Successful extubation from CV was associated with GA, BW, delivery method, sex, 5 min Apgar score and CRIB II score. For the infants extubated from HFOV, there was no significant difference in characteristics at birth between those with successful and unsuccessful attempts.

Extubation characteristics

Extubation characteristics of infants with successful or failed first extubation attempts are presented in table 2. Among extubations from CV, 11 (4%) infants received synchronised intermitted mandatory ventilation, 230 (89%) received synchronised positive pressure ventilation or pressure support ventilation and 18 (7%) infants received neurally adjusted ventilatory assist prior to the extubation attempt. A total of 123 (47%) infants received VTV.

Unadjusted analyses showed significantly higher weight, higher pH, lower oxygen and lower mean RSS before extubation but no other differences in objective measures of respiratory illness or medical treatment between successfully extubated infants and those who failed. All infants received either bilevel positive airway pressure or nasal continuous positive airway pressure (NCPAP) immediately after extubation, with NCPAP as the foremost chosen respiratory support.

Adjusted analyses

In a multivariable analysis of extubation from CV, pre-extubation FiO_2 ≤0.35, 5 min Apgar score >5, higher GA, female sex and higher postnatal age at the extubation day remained predictive of successful extubation (table 3). The OR of successful extubation was 6.3 (95% CI 2.5 to 16.0) if the received pre-extubation FiO_2 ≤0.35 prior to the attempt. In multivariable analysis of extubation from HFOV, pre-extubation FiO_2 ≤0.35 remained predictive of successful extubation.

The predictors of successful extubation were combined in a model to construct a receiver operating characteristic curve for the two prediction models. Internal validation of the model for extubation from CV showed the optimism corrected (a measure of model performance after internal validation) R^2 at 0.28, corrected area under the curve at 0.77 and calibration slope at 0.89. The internal validation of the model for extubation from HFOV identified large model overfitting (R^2=0.23, area under the curve=0.76, calibration slope=0.76). Multivariable analyses performed separately for female and male infants, as well as for infants with late first extubation attempt (>14 days postnatal age) are shown in online supplemental tables 1 and 2, respectively.

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Table 1 Characteristics at birth of infants extubated from conventional ventilation and high-frequency ventilation at first extubation attempt, n=316

	Extubated from CV			Extubated from HFOV		
Variable	Successful, n=140	Failed, n=121	P value	Successful, n=33	Failed, n=22	P value
GA, weeks, median (IQR)	25.1 (24.4–25.5)	24.4 (23.5–25.1)	<0.001*	24.4 (23.5–25.1)	24.1 (23.5–24.4)	0.13*
Birth weight g, mean (SD)	695 (147)	651 (124)	0.01	641 (127)	628 (118)	0.69
Complete ANS course†, n (%)	84/133 (63)	69/116 (59)	0.60	20/31 (65)	10/20(50)	0.39
Vaginal delivery, n (%)	86 (61)	91 (75)	0.02*	20 (61)	16 (73)	0.40*
Male sex, n (%)	64 (46)	77 (64)	0.004*	9 (27)	10 (45)	0.25*
Female sex, n (%)	76 (54)	44 (36)		24 (73)	12 (55)	
Multiple birth, n (%)	32 (23)	33 (27)	0.48	10 (30)	6 (27)	1.0
SGA, n (%)	29 (21)	21 (17)	0.35*	6 (18)	4 (18)	1.0
RSS at birth‡, median (IQR)	2.1 (1.7–2.9)	2.3 (1.9–2.9)	0.14	2.6 (1.9–4.0)	3.1 (2.0–4.6)	0.39
Apgar <5 at 5 min, n (%)	15 (11)	29 (24)	0.01*	9 (27)	7 (32)	0.77*
CRIB II>14, n (%)	64 (48)	74 (64)	0.02*	20 (61)	14 (67)	0.78*
Surfactant <first 30 min of life, n (%)	137/139 (99)	119/120 (99)	1.0	31 (94)	22 (100)	0.51
LISA, n (%)	19 (14)	9 (7)	0.16	0 (0)	2 (9)	0.16

*Variables included in multivariable analysis.
†A complete ANS course was defined as when the first dose was administered at least 24 hours before birth. Time of first dose was not registered in 16 (4.9%) infants.
‡RSS was calculated as a product of MAP and fraction of inspired oxygen. Mean RSS at birth was calculated for each infant's first 6 hour of life.
ANS, antenatal steroids; CRIB, Clinical Risk Index for Babies; CV, conventional ventilation; GA, gestational age; HFOV, high frequency oscillatory ventilation; LISA, less invasive surfactant administration; MAP, mean airway pressure; RSS, Respiratory Severity Score; SGA, small for gestational age.

DISCUSSION

In this population-based study of EP infants clinically judged ready for extubation, we found that successful extubation from CV was associated with pre-extubation FiO_2 ≤0.35, a 5 min Apgar score >5, higher GA, female sex and higher postnatal age. Successful extubation from HFOV was associated with pre-extubation FiO_2 ≤0.35. It is important to note that associations between these factors and the results of extubation attempts may be an addition to, not replacement for, clinical judgement.

Our results align with Gupta *et al*, with a higher GA, higher postnatal age, and lower pre-extubation FiO_2 being predictive of successful extubation.[18] In contrast, pre-extubation pH, weight at extubation and RSS at birth did not independently predict extubation success in our cohort. The differences in the findings may be related to differences in the populations explored. Our population only included EP infants <26 weeks GA in a national cohort, whereas the Gupta study was not population based and included more mature infants. In contrast to the results of Kidman *et al*,[19] we did not identify associations with successful extubation and MAP, a finding that probably reflects the clinical evaluation prior to the extubation attempt because all the participating units reported PIP (to achieve normal tidal volume) and oxygen requirement as clinical considerations for extubation readiness.

In several previous studies, low pre-extubation FiO_2 has been reported as predictive of extubation success.[9 18 25] We suggest that a cut-off for pre-extubation FiO_2 at ≥0.35 is a clinically relevant predictor indicating a high risk for extubation failure. In addition to oxygen requirement, clinicians consider blood gas measurements including pCO_2 prior to extubation. Earlier studies have identified lower pre-extubation pCO_2 as an important predictor of successful extubation,[8] as hypercapnia could be an indication of insufficient respiratory drive or low lung compliance. In this study, the pre-extubation pCO_2 was not significantly lower in infants with extubation success compared with those who failed. These results may indicate that clinicians attempt extubation when infants' blood gas measurements are within the normal range.

Similar to previous studies, a 5 min Apgar score >5 was associated with extubation success in the present research.[9 26] The value of the Apgar score in EP infants has been questioned because the frequency of low Apgar scores increases with decreasing GA and may reflect immaturity in general.[27] The relevance of the Apgar score in clinical practice regarding the evaluation of extubation readiness is also questionable. We find the association

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Table 2 Characteristics at first extubation attempt, n=316

	Extubated from CV			Extubated from HFOV		
Variable	Successful, n=140	Failed, n=121	P value	Successful, n=33	Failed, n=22	P value
PNA in days, median (IQR)	5 (2–19)	7 (3–16)	0.14*	18 (9–32)	15 (8–25)	0.46*
PMA in weeks, median (IQR)	25.9 (25.4–27.1)	25.6 (24–9–26.7)	0.004	27.3 (25.8–28.2)	25.9 (25.1–28.0)	0.13
Weight g, median (IQR)	740 (620–864)	675 (607–780)	0.02	792 (653–924)	800 (653–1000)	0.97
Growth course g†, median (IQR)	0 (-41–129)	1 (-31–112)	0.87*	118 (37–305)	148 (43–300)	0.87*
Pre-extubation VI‡, median (IQR)	1.9 (1.2–2.4)	1.9 (1.3–2.7)	0.32	NA	NA	NA
Pre-extubation pH§, median (IQR)	7.30 (7.26–7.34)	7.28 (7.23–7.33)	0.04	7.27 (7.19–7.35)	7.26 (7.20–7.33)	0.73
Pre-extubation pCO_2§¶ median (IQR)	6.2 (5.5–7.0)	6.3 (5.7–7.5)	0.06	6.6 (6.3–7.5)	6.6 (5.4–8.0)	0.67
Pre-extubation BE‡, median (IQR)	−3.6 (-6.3 to -1.1)	−5.1 (-6.8 to -1.6)	0.18	−2.5 (-7.0–1.5)	−2.6 (-8.2–0.6)	0.51
Pre-extubation FiO_2, median (IQR)	0.23 (0.21–0.28)	0.25 (0.21–0.33)	0.006*	0.28 (0.24–0.31)	0.33 (0.29–0.44)	0.001*
Pre-extubation RSS**, median (IQR)	1.9 (1.7–2.3)	2.1 (1.7–2.9)	0.005	2.8 (2.2–3.4)	3.3 (2.8–4.0)	0.02
Pre-extubation set ventilation rate, median (IQR)	35 (30–40)	35 (30–45)	0.03	NA	NA	NA
Pre-extubation MAP††, mean (SD)	8.1 (0.13)	8.4 (0.11)	0.07*	9.7 (0.30)	10.2 (0.44)	0.40*
Pre-extubation PIP‡‡, median (IQR)	15 (12–17)	15 (13–16)	0.95	NA	NA	NA
Caffein administration at the day of extubation, n (%)	137 (98)	120 (99)	0.63	32 (97)	22 (100)	1.0
Caffein mg/kg/day, median (IQR),	9.3 (6.0–10.8)	9.8 (7.1–12.4)	0.10	7.5 (6.2–9.8)	8.5 (5.9–16.3)	0.42
Steroid administration at the day of extubation, n (%)	37 (26)	30 (25)	0.78	21 (64)	11 (50)	0.41

*Variables included in multivariable analysis.
†Growth course is the calculated difference between weight at the intubation day and the day of extubation.
‡VI was calculated as partial pressure of carbon dioxide (pCO_2) in arterial, venous or capillary blood multiplied by the ventilator set rate multiplied by the difference between PIP and positive end expiratory pressure, all divided by 1000.
§Measured in arterial, capillary or venous blood samples.
¶The pCO_2 values are given in kilopascal (multiplication by 7.50062 provide values in milimetres of mercury).
**RSS was calculated as a product of MAP and FiO_2. Pre-extubation RSS was calculated based on the last 6 hours before extubation.
††Presented as mean MAP last 6 hours before extubation, missing values in 4 (7%) infants extubated from HFOV.
‡‡PIP derived by a set pressure for infants on pressure limited ventilation, and measured PIP for infants on volume target ventilation.
BE, base excess; CV, conventional ventilation; FiO_2, fraction of inspired oxygen; HFOV, high-frequency oscillatory ventilation; MAP, mean airway pressure; NA, not applicable; pH, potential of hydrogen; PIP, peak inspiratory pressure; PMA, postmenstrual age; PNA, postnatal age; RSS, Respiratory Severity Score; VI, ventilation index.

between Apgar score and the lack of association between CRIB II and extubation outcome surprising. Notably, our findings indicate that the association between the general condition at birth and extubation outcome may be reserved for female infants.

The relationship between extubation success and increased GA is well established.[8 21 28–30] A likelihood of extubation success for infants born at higher GA could be explained by advanced lung maturity with increasing GA. However, GA was not independently predictive of extubation success for infants extubated from HFOV in our study. HFOV is commonly used as a rescue treatment for infants where CV does not provide sufficient respiratory support. In our cohort, infants extubated from HFOV had a significantly higher postnatal age when clinicians first attempted extubation. In addition, the proportion of infants who received corticosteroids on the extubation day was higher among infants extubated from HFOV compared with infants extubated from CV. These findings may indicate that infants extubated from HFOV had more severe pulmonary morbidity compared with infants extubated from CV, because in Norwegian NICUs

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Table 3 Adjusted markers of successful extubation for infants extubated from conventional ventilation (CV) and for infants extubated from HFOV

Effect	OR	95% CI	P value	Coef.	Adj. coef.
Extubation from CV, n=261					
GA, weeks	3.1	2.03 to 4.58	<0.001	1.19	1.05
Female sex	2.4	1.34 to 4.16	0.003	0.87	0.77
Apgar >5 at 5 min of age	3.3	1.46 to 7.25	0.004	1.18	1.05
Age at extubation, days	1.1	1.02 to 1.08	<0.001	0.06	0.05
Pre-extubation FiO_2 ≤0.35	6.3	2.51 to 16.00	<0.001	1.92	1.70
MAP at extubation	0.8	0.66 to 1.06	0.135	−0.18	−0.16
Extubation from HFOV, n=55					
Female sex	2.6	0.71 to 9.71	0.15	0.97	0.73
Age at extubation, days	1.1	1.00 to 1.13	0.08	0.06	0.05
Pre-extubation FiO_2 ≤0.35	8.6	1.76 to 42.19	0.008	2.15	1.63
MAP at extubation	0.6	0.38 to 1.00	0.05	−0.49	−0.37

Coef, coefficient; FiO_2, fraction of inspired oxygen; GA, gestational age; HFOV, high-frequency oscillatory ventilation; MAP, mean airway pressure.

postnatal corticosteroid therapy are usually reserved infants considered in high risk of bronchopulmonary pulmonary disease and prolonged MV treatment after 10–14 days of age.

We found that females were more often successfully extubated than males. Male sex has previously been identified as a risk factor for longer hospital stay, higher postmenstrual age at discharge and lower survival.[31] In addition, we previously reported that males had significantly longer cumulative MV compared with females.[32]

Our study has limitations. We relied on retrospective data retrieved from medical records when infants were considered extubation ready. Some potentially useful variables (eg, blood gas values and tidal values) were missing and not included. Furthermore, information on maternal health and infant infection status at birth which could affect the respiratory trajectory and first extubation outcome were not available.

The strength of our study is the inclusion of a complete national cohort of premature infants born at <26 weeks GA were we provide descriptions of extubation outcomes for infants extubated from CV and HFOV. In addition to the already established clinical evaluation of lung compliance, respiratory drive and oxygen demand, clinicians may also consider the infants' GA, postnatal age, sex and general condition at birth in the evaluation before first extubation of the smallest EP infants.

CONCLUSION

In this population-based study exploring first extubation attempts among EP infants <26 weeks GA, 55% remained successfully extubated within the first 72 hours. Our results suggest that additional emphasis on oxygen requirement, sex and general condition at birth may further increase extubation success when clinicians are about to extubate the most immature infants for the first time.

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