The Impact of Time Interval between Extubation and Reintubation on Death or Bronchopulmonary Dysplasia in Extremely Preterm Infants

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Objective To explore the relation between time to reintubation and death or bronchopulmonary dysplasia (BPD) in extremely preterm infants.

Study design This was a subanalysis from an ongoing multicenter observational study. Infants with birth weight ≤1250 g, requiring mechanical ventilation, and undergoing their first elective extubation were prospectively followed throughout hospitalization. Time to reintubation was defined as the time interval between first elective extubation and reintubation. Univariate and multivariate logistic regression analyses were performed to evaluate associations between time to reintubation, using different observation windows after extubation (24-hour intervals), and death/BPD (primary outcome) or BPD among survivors (secondary outcome). aORs were computed with and without the confounding effects of cumulative mechanical ventilation duration.

Results Of 216 infants included for analysis, 103 (48%) were reintubated at least once after their first elective extubation. Reintubation was associated with lower gestational age/weight and greater morbidities compared with infants never reintubated. After adjusting for confounders, reintubation within observation windows ranging between 24 hours and 3 weeks postextubation was associated with increased odds of death/BPD (but not BPD among survivors), independent of the cumulative mechanical ventilation duration. Reintubation within 48 hours from extubation conferred higher risk-adjusted odds of death/BPD vs other observation windows.

Conclusions Although reintubation after elective extubation was independently associated with increased likelihood of death/BPD in extremely preterm infants, the greatest risk was attributable to reintubation within the first 48 hours postextubation. Prediction models capable of identifying the highest-risk infants may further improve outcomes. *(J Pediatr 2019;205:70-6).*

Extremely preterm infants are often reintubated after a trial of extubation. Based on recent cohort studies, nearly 50% of very low birth weight and 60%-70% of extremely low birth weight infants require resumption of mechanical ventilation at least once during their hospitalization.[1-3] However, the time to reintubation, referring to the time interval between mechanical ventilation courses, can range anywhere from a few hours to several weeks after extubation.[1]

Although prolonged mechanical ventilation exposure is a well-established risk factor for death and/or bronchopulmonary dysplasia (BPD) in these infants,[2,4,5] the direct impact of reintubation on respiratory outcomes is less well understood. Recent subanalyses from 2 large randomized controlled trials showed that reintubation within 5 and 7 days after extubation independently increased respiratory morbidities and mortality.[6,7] In contrast, the only study that adjusted for the cumulative duration of mechanical ventilation found that a single reintubation any time after extubation did not increase the risk-adjusted odds of BPD among survivors.[2] Importantly, all studies to date have used very different observation windows to decide which reintubations were considered clinically relevant, and made the assumption that all included reintubations, irrespective of their timing, would affect outcomes equally. It remains unclear whether a reintubation occurring within hours from extubation would have the same clinical implications as a reintubation occurring days or weeks later. In adults, both prompt and delayed reintubations have been associated with increased mortality.[8-10] Therefore, we sought to explore associations between time to reintubation and the composite outcome of death or BPD in a large prospective cohort of extremely preterm infants.

APEX	Automated Prediction Tool of Extubation Readiness in Extremely Preterm Infants
BPD	Bronchopulmonary dysplasia
NICUs	Neonatal intensive care units

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Funded by an operational grant from the Canadian Institutes of Health Research (to R.K., G.S., K.B., D.P., L.K., S.C.). The funding body did not have a role in the design and collection, analysis or interpretation of the data. The authors declare no conflicts of interest.

Portions of this study were presented at the Pediatric Academic Societies annual meeting, May 6-9, 2017, San Francisco, California.

https://doi.org10.1016/j.jpeds.2018.09.062

Methods

This study was an exploratory analysis of an ongoing multicenter observational study aiming to develop an Automated Prediction Tool of Extubation Readiness in Extremely Preterm Infants (APEX) study.[11] Infants included were enrolled between September 2013 and June 2017 at 5 different neonatal intensive care units (NICUs) in Canada and the US. The study was approved by each institution's Ethics Review Board, and written consent was obtained from the parents.

The APEX study rationale and protocol are described in detail elsewhere.[11] In brief, infants with birth weight ≤1250 g, requiring mechanical ventilation, and undergoing their first elective extubation were included. Exclusion criteria were congenital anomalies or heart defects, extubation from high frequency ventilation, extubations directly to low flow nasal cannula or no respiratory support, and deaths prior to extubation. All decisions regarding weaning from mechanical ventilation, extubation, and reintubation were made by the treating team and not influenced by the study.

The APEX study includes a large database of clinical variables prospectively collected by trained abstractors at various time points throughout hospitalization in the NICU. Details on data collection and quality control methods are described elsewhere.[11,12] For the purpose of this study, the following variables were evaluated:

Exposure

For each infant reintubated, "time to reintubation" was computed as the date and time of reintubation minus the date and time of the first elective extubation. Using that information, the exposure of interest was defined as reintubation within different observation windows following extubation. Each observation window was binned into 24-hour intervals, thus, creating a broad range of exposures going from "reintubation within 24 hours after extubation" to "reintubation any time during NICU hospitalization."

Outcomes

The primary outcome was the composite of death or moderate-to-severe BPD, defined as the need for any supplemental oxygen and/or any type of invasive or noninvasive respiratory support at 36 weeks postmenstrual age.[13] Noninvasive respiratory support included any form of continuous positive airway pressure, nasal intermittent positive pressure ventilation, or heated humidified high flow nasal cannula. The secondary outcome was BPD among infants surviving to discharge from the NICU.

Confounders

The cumulative duration of mechanical ventilation was selected a priori as an important confounder for inclusion in the final statistical model. From the database, a day of mechanical ventilation corresponded to a calendar day in which mechanical ventilation was the most employed type of respiratory support. Other potential confounding variables included gestational age, birth weight, sex, study site, small for gestational age (defined as birth weight below the 10th percentile using a Canadian reference growth curve),[14] antenatal steroids, cord pH, 5-minute Apgar score, intubation in the delivery room, surfactant use, caffeine use, postmenstrual age and weight at extubation, pre-extubation hemoglobin (if sampled within the preceding 24 hours), pre-extubation blood gas (pH and pCO_2) and ventilator measures (mean airway pressure and fraction of inspired oxygen), and postextubation respiratory support. Outcomes at discharge comprised postnatal steroids use, patent ductus arteriosus, necrotizing enterocolitis (modified Bell's stage IIA or above requiring medical or surgical intervention),[15] intraventricular haemorrhage of any grade, and culture-proven postnatal infection (bloodstream, urine or cerebrospinal fluid).

Statistical Analyses

All analyses were conducted using MATLAB (R2016a; The MathWorks, Natick, Massachusetts). Patient characteristics were first compared between infants reintubated and those never reintubated using Wilcoxon rank sum test (for continuous variables) and χ^2 or Fisher exact tests (for categorical variables). Amongst infants requiring reintubation, a cumulative frequency graph was plotted to present the number of infants reintubated within each observation window following extubation and their respective outcomes (death, BPD, or no BPD). Also, the cumulative proportion of infants that developed death/BPD was determined as a function of time to reintubation. Univariate and multivariate logistic regression analyses were used to evaluate for associations between time to reintubation and outcomes. To construct the multivariate logistic regression model, clinically relevant variables with $P < .20$ in the bivariate analysis were assessed using stepwise regression; only those variables with $P < .05$ were included in the final model. aOR and 95% CI were then computed using 2 models: model 1 adjusted for all variables obtained in the stepwise regression, and model 2 additionally accounted for the confounding effect of cumulative mechanical ventilation duration. The correlation between time to reintubation and cumulative mechanical ventilation duration was determined using Spearman rank correlation, and an interaction term between the exposure of interest and cumulative mechanical ventilation duration was incorporated into the second multivariate model if it was shown to be statistically significant ($P < .05$).

Results

A total of 216 infants were included, of which 103 (48%) were reintubated at least once during hospitalization (**Figure 1**; available at www.jpeds.com). **Table I** compares the characteristics of infants who were reintubated or not. Infants requiring reintubation were significantly smaller and more immature at birth compared with those never reintubated. At the time of extubation, they also had significantly lower weight and postmenstrual age, were exposed to more days on mechanical ventilation, and received a higher fraction of inspired oxygen. There were no significant differences between groups with regards to the type of immediate postextubation respiratory support used. By discharge from the NICU, infants requiring

Table I. Population characteristics

Variables	Reintubated (n = 103)	Never reintubated (n = 113)	*P* value
Demographics			
Gestational age, wk	25.6 [24.6-26.6]	27 [25.3-28.3]	<.001
Birth weight, g	760 [669-900]	945 [750-1116]	<.001
Male sex	56 (54)	56 (50)	.48
Small for gestational age	15 (15)	15 (13)	.78
Antenatal steroids	92 (89)	104 (92)	.49
Apgar score 5 min*	6 [5-8]	7 [5-8]	.82
Intubation in delivery room	63 (61)	47 (42)	.004
Surfactant	97 (94)	108 (96)	.64
Caffeine	101 (98)	109 (96)	.69
Pre-extubation			
Postmenstrual age, wk	27.6 [26.6-29]	28.7 [27.4-30]	<.001
Weight, g	860 [730-974]	1040 [868-1153]	<.001
mechanical ventilation d	8 [3-25]	4 [2-20]	.04
pH†	7.34 [7.3-7.38]	7.33 [7.29-7.38]	.45
pCO_2, mm Hg†	44 [37-52]	44 [39-50]	.8
Mean airway pressure, cmH_2O‡	7 [6.2-8.4]	6.9 [6.2-7.8]	.25
Fraction of inspired oxygen	0.25 [0.21-0.28]	0.21 [0.21-0.25]	<.001
Hemoglobin (≤24 h), g/L§	130 [121-143]	138 [121-157]	.07
Postextubation			
CPAP	51 (49)	63 (56)	.36
NIPPV	48 (47)	40 (35)	.09
HHHFNC	4 (4)	10 (9)	.14
Outcomes by discharge			
Additional mechanical ventilation d	12 [6-26]	0 [0-0]	<.001
Cumulative mechanical ventilation d	31 [14-40]	4 [2-20]	<.001
Postnatal steroids	66 (64)	25 (22)	<.001
Intraventricular hemorrhage	41 (40)	32 (28)	.08
Patent ductus arteriosus	68 (66)	50 (44)	.001
Necrotizing enterocolitis	23 (22)	7 (6)	<.001
Postnatal infection	49 (48)	33 (29)	.01

CPAP, continuous positive airway pressure; *HHHFNC*, heated humidified high flow nasal cannula; *NIPPV*, nasal intermittent positive airway pressure.
Values are expressed as medians [IQR] or n (%).
*Data available for 102 reintubated and 112 never reintubated infants.
†Data available for 97 reintubated and 97 never reintubated infants.
‡Data available for 102 reintubated infants.
§Data available for 53 reintubated and 51 never reintubated infants.

reintubation had received a median of 12 additional days of mechanical ventilation (IQR 6-26 days), and had significantly greater postnatal steroid use, higher rates of patent ductus arteriosus, necrotizing enterocolitis, and infection compared with infants never reintubated.

Figure 2 displays the cumulative number of infants reintubated and their respective outcomes (death, BPD, or survival without BPD) as a function of time to reintubation. Out of 103 infants, 35 (34%) were reintubated within 3 days, 61 (59%) within 7 days, and 77 (75%) within 14 days after the first elective extubation. The cumulative probability of developing death/BPD among reintubated infants was dependent on the observation window used: the shorter the window, the higher the probability (solid line, **Figure 2**). That is, although the overall probability of death/BPD was 83% for all reintubated infants, it was as high as 93% when limiting the observation window to infants reintubated within 48 hours after extubation. By contrast, the probability of death/BPD amongst infants never reintubated was 38%.

Unadjusted and adjusted associations between time to reintubation for different observation windows after extubation, and outcomes are shown in **Table II**. Adjustments were made for birth weight, study site, postnatal infection, postnatal steroids and necrotizing enterocolitis in both multivariate models, but model 2 additionally accounted for cumulative mechanical ventilation duration. Results for all other independent variables included in the multivariate models are shown in **Table III** (available at www.jpeds.com). There was no correlation (correlation coefficient r = −0.04) and no interaction ($P > .05$) between time to reintubation and cumulative mechanical ventilation days.

In comparison to infants never reintubated, reintubation within any observation window after extubation was associated with significantly higher odds of the primary outcome of death/BPD in both univariate analysis and model 1 of the multivariate analysis. After accounting for the cumulative duration of mechanical ventilation (model 2), statistical significance persisted for the most part, but was lost once the observation window was extended to include all reintubations. Interestingly, as illustrated in **Figure 3**, the risk-adjusted odds appeared to be disproportionately higher for reintubations occurring within the first 24 and 48 hours after extubation compared with any other window of observation, and gradually decreased thereafter. Also, total mechanical ventilation duration remained significantly associated with increased odds of death/BPD in the final model (OR 1.08; 95% CI 1.03-1.13).

In the univariate analysis, reintubation within any observation window after extubation was associated with significantly greater odds of BPD among survivors when compared with infants never reintubated. After accounting for confounders (including the effects of cumulative mechanical ventilation duration), reintubation was no longer associated with an increase in the risk-adjusted odds of BPD. In contrast, total mechanical ventilation duration remained significantly associated with increased odds of BPD among survivors in the final model (OR 1.13; 95% CI 1.06-1.21).

In an attempt to better understand why time to reintubation was independently associated with increased death/BPD but not BPD among survivors, a post-hoc evaluation of the causes of all infant deaths and their relationship to timing of extubation and reintubation was performed. There were a total of 10 infant deaths in the cohort: 1 infant never required reintubation, 3 were reintubated within 24 hours, 3 between 48 hours and 7 days, and 3 after 7 days from extubation. This meant that reintubation within each of those time periods was associated with a 14%, 9%, and 7% risk of death, respectively (compared with a 1% mortality for infants never reintubated). Among infants reintubated within the first 24 hours, the 3 deaths were attributed to (1) pulmonary hemorrhage immediately postextubation, (2) grade 4 intraventricular hemorrhage detected on a cranial ultrasound after reintubation (followed by withdrawal of life-sustaining therapy), and (3) fulminant necrotizing enterocolitis that became clinically manifest a few hours after extubation. The characteristics

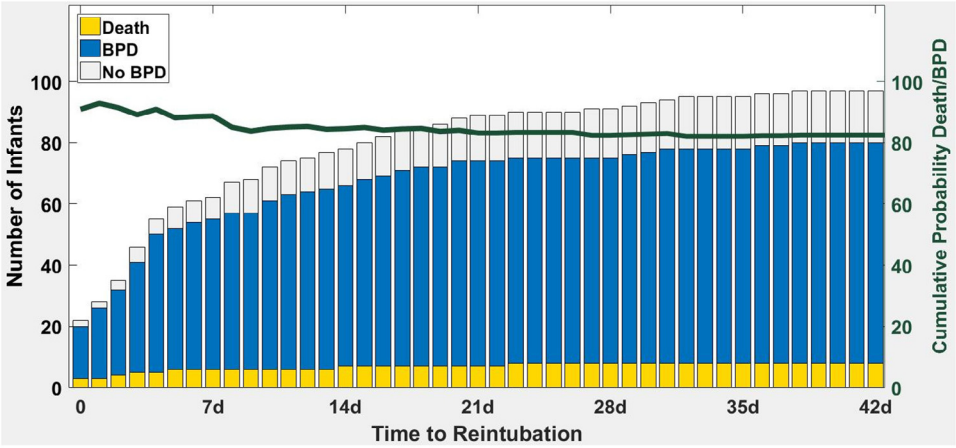

Figure 2. Cumulative number of infants reintubated and cumulative probabilities of death/BPD as a function of time to reintubation. An additional 6 infants were reintubated beyond 42 days after their first planned extubation. The solid green line represents the cumulative probability of death/BPD as a function of the time interval between the first elective extubation and reintubation.

of all remaining deaths are available in **Table IV** (available at www.jpeds.com).

Finally, given the high risk of death/BPD identified for reintubations within the first 48 hours after extubation, a second post-hoc analysis was undertaken to determine whether other markers of illness severity were present among these infants. The latter had a median postmenstrual age of 27.4 weeks (IQR 26.5-28.4), weighed 820 g (IQR 690-950), and were exposed to 11 days of mechanical ventilation (IQR 2-25) at the time of their first extubation attempt. When comparing the pre-extubation characteristics of these infants with those of infants reintubated between 48 hours and 7 days after extubation (using Wilcoxon rank-sum, χ^2, or Fisher exact tests), no statistically significant differences could be detected (**Table V**; available at www.jpeds.com). Moreover, there was no significant difference between groups in the number of intubation attempts required at the time of reintubation (reintubation within 48 hours: median 1, IQR 1-2; reintubation between 48 hours and 7 days: median 1, IQR 1-3, $P = 1$).

Discussion

In this exploratory analysis from a large prospective study, we found that time to reintubation independently modulated the odds of the combined outcome of death/BPD, conferring the greatest risk when reintubation occurred within 48 hours from

Table II. Adjusted odds of death/BPD and BPD among survivors as a function of reintubation within different observation windows after extubation

Outcomes/time of reintubation	Univariate	Multivariate model 1	Multivariate model 2
Death/BPD			
Never reintubated	1 [Reference]	1 [Reference]	1 [Reference]
≤24 h	16.28 (3.59-73.76)	12.44 (1.77-87.67)	12.29 (1.27-118.66)
≤48 h	21.16 (4.74-94.47)	13.17 (1.93-89.61)	12.76 (1.38-117.62)
≤72 h	17.36 (4.98-60.61)	7.98 (1.64-38.84)	6.12 (1.05-35.77)
≤5 d	16.28 (5.99-44.27)	6.57 (1.88-22.92)	4.40 (1.17-16.55)
≤7 d	12.56 (5.21-30.25)	5.47 (1.76-16.98)	4.03 (1.21-13.39)
≤14 d	8.82 (4.26-18.25)	3.85 (1.44-10.30)	2.92 (1.02-8.34)
≤21 d	8.60 (4.32-17.15)	3.88 (1.53-9.85)	3.00 (1.10-8.18)
Anytime	7.69 (4.06-14.55)	3.07 (1.29-7.26)	2.37 (0.94-5.98)
BPD among survivors			
Never reintubated	1 [Reference]	1 [Reference]	1 [Reference]
≤24 h	14.17 (3.09-64.99)	3.53 (0.64-19.52)	1.44 (0.22-9.38)
≤48 h	19.17 (4.26-86.21)	3.99 (0.74-21.54)	1.60 (0.25-10.14)
≤72h	15.56 (4.42-54.74)	3.33 (0.78-14.2)	1.33 (0.27-6.66)
≤5 d	15.00 (5.49-41.02)	3.90 (1.13-13.41)	1.56 (0.40-6.06)
≤7 d	11.43 (4.71-27.71)	3.32 (1.05-10.47)	1.56 (0.43-5.73)
≤14 d	8.19 (3.94-17.06)	2.67 (0.96-7.43)	1.48 (0.45-4.86)
≤21 d	7.98 (3.98-15.99)	2.78 (1.05-7.35)	1.51 (0.48-4.72)
Anytime	7.04 (3.69-13.40)	2.09 (0.85-5.16)	1.09 (0.38-3.15)

Results are expressed as OR (95% CI) and models were adjusted for birth weight, study site, postnatal infection, postnatal steroids and necrotizing enterocolitis. Model 2 was additionally adjusted for total mechanical ventilation days.

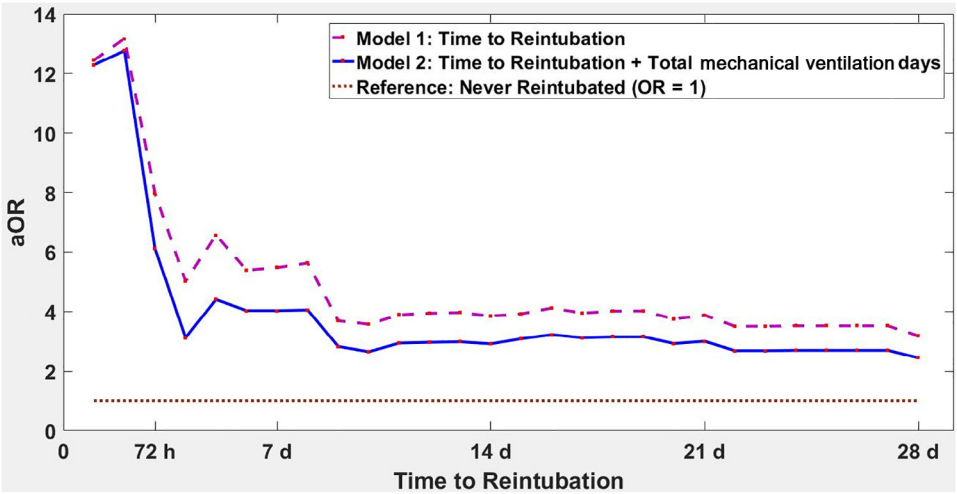

Figure 3. aOR of Death/BPD as a function of time to reintubation. Each red square represents the adjusted odds of death/BPD for each time frame to reintubation, in relation to infants never reintubated. Models were adjusted for birth weight, site, postnatal infection, necrotizing enterocolitis, and postnatal steroids.

extubation. This significance persisted even after adjusting for the effect of cumulative mechanical ventilation duration. In contrast, reintubation, irrespective of the observation window used, did not increase the risk-adjusted odds of BPD among survivors. Together, these results provide novel insight to the importance of timing when evaluating the clinical implication of reintubations in extremely preterm infants.

In recent years, 3 large studies have investigated the associations between reintubation and death and/or respiratory morbidities in extremely preterm infants.[2,6,7] In a secondary analysis from a randomized trial comparing postextubation high flow nasal cannula with continuous positive airway pressure, Manley et al demonstrated that infants reintubated within 7 days after extubation were significantly more likely to die or require prolonged respiratory support and hospitalization.[6] In another secondary analysis from the Surfactant, Positive Pressure, and Oxygenation Randomized Trial, Chawla et al showed that infants reintubated within 5 days from extubation had significantly greater risk of death, BPD, death/BPD and prolonged length of respiratory support and hospitalization.[7] In contrast, in a large retrospective cohort study including more than 3000 extremely low birth weight infants, Jensen et al found that the need for a second course of mechanical ventilation any time after extubation did not increase the risk of BPD (among survivors), tracheostomy, or supplemental oxygen at discharge once adjustments were made for the total mechanical ventilation duration.[2] In trying to synthesize results from the aforementioned studies, some limitations emerge. First, each study used a different observation window to delineate which reintubations were considered clinically pertinent for evaluation. Second, studies made the presumption that all reintubations captured within their observation window would confer equal risks to the outcomes of interest. Lastly, some studies did not adjust for the cumulative mechanical ventilation duration in their respective analyses, making it unclear if reintubation truly affected outcomes independently or if the adverse effects were mediated by the resumption of mechanical ventilation. Thus, we attempted to systematically explore these issues using our study cohort, and focused primarily on the composite outcome of death/BPD.

In our cohort, the probability of death or BPD was highest for infants reintubated within the first few days after extubation. As the time interval between extubation and reintubation increased, a greater proportion of infants survived to discharge without BPD. From these findings, it is not surprising that the choice of observation window had a marked effect on the strength of the association between reintubation and death/BPD. That is, limiting the observation window to the first 48 hours after extubation led to the highest risk-adjusted odds of death/BPD, whereas extending the window to include more distant reintubations led to gradually weaker (and eventually nonsignificant) associations. As a result, a study evaluating all reintubations during hospitalization may dilute or mask the adverse effects conferred by earlier events, thereby providing a misleading reassurance about reintubation.

Not all reintubations conferred equal risks of death/BPD. The need for reintubation within 48 hours postextubation was associated with disproportionately higher risk-adjusted odds of death/BPD compared with any other observation window. This suggests that even though reintubation within broader observation windows (eg, 7 or 14 days) resulted in independently increased risk of death/BPD, it is likely that the significance was driven by earlier reintubations.

The characteristics of those infants who required rapid reintubation were evaluated in a post-hoc analysis. A total of 28 infants were reintubated within 48 hours from extubation, out of which 26 (93%) died or developed BPD. These infants had no distinctive pre-extubation characteristics (postmenstrual age, weight, ventilatory settings, blood gases, or other comorbidities) (ie, were no less "ready" for a trial of

extubation). Furthermore, we found that one-third of all infant deaths in our cohort had required a reintubation within 24 hours from extubation (more specifically at 30 minutes, 7 hours, and 8 hours after extubation), thus, conferring a 14% risk of mortality. Careful scrutiny of the reintubations, as well as extrapolation from adult studies, leads us to speculate on some biologically plausible mechanisms that may have contributed to those results.

One likely explanation is that infants who promptly failed extubation represented an inherently sicker group. Indeed, when compared with infants never reintubated, those who required a second course of mechanical ventilation were significantly smaller, less mature, and had more comorbidities. Altogether, these risk factors frequently result in the need for mechanical ventilation resumption and are also associated with increased mortality and BPD. Thus, the fact that early reintubation (≤48 hours) continued to have an independent effect on death/BPD even after adjusting for confounders may have simply reflected an additional (independent) marker of illness severity. In our post-hoc analysis, we further attempted to isolate pre-extubation risk factors specific to those infants who were reintubated within 48 hours from extubation (**Table V**). Although no statistically significant factors were identified, this could have been due to the small sample size and large variance of some of the variables (eg, pre-extubation mechanical ventilation days).

Another hypothesis is that infants promptly reintubated (within 48 hours from extubation) had a clinical deterioration that directly resulted from removal of the ventilatory support provided during mechanical ventilation. In adult studies, it is well established that the addition of positive end-expiratory pressure and/or pressure support during mechanical ventilation can significantly decrease work of breathing, reduce pulmonary wedge pressure and improve left ventricular performance.[16-19] Although most patients are capable of compensating for the transiently increased mechanical load that follows extubation, a minority may not adequately cope, thereby leading to rapid cardiorespiratory compromise and potentially catastrophic (sometimes fatal) consequences.[10,18] Although concrete evidence for this is missing in the extreme preterm population, it is plausible that removal of invasive ventilatory support, albeit "minimal," may have had clinically deleterious effects in the most fragile infants.

Finally, the technique of intubation in itself has been linked with increased complications, ranging from transient hemodynamic instability to cardiorespiratory arrest or death.[20] Intubations with higher number of attempts, and those performed without premedication use or in an emergent setting all impart a greater risk of serious adverse events.[20,21] From our study, although we could not ascertain most of the above risk factors, it is conceivable that infants who promptly failed their extubation attempt may have required more emergent interventions.

Reintubation unavoidably leads to additional exposure to mechanical ventilation. In our cohort, infants requiring reintubation received a median of 12 additional mechanical ventilation days, a finding consistent with previous data.[2] Each additional week of mechanical ventilation incrementally increases the risk of BPD and other respiratory morbidities.[2,4] For that reason, it is important to adjust for its confounding effects when evaluating the independent effects of reintubation on respiratory outcomes. In our multivariate analyses, adjustments for total mechanical ventilation duration consistently weakened the association between reintubation (at observation windows >48 hours) and death/BPD, and eliminated all associations between reintubation (at any observation window) and BPD among survivors. Thus, in concordance with results obtained by Jensen et al, our findings indicate that the increased risk of death or BPD conferred by most reintubations (especially those beyond 48 hours from extubation) is likely mediated by prolonged exposure to mechanical ventilation.[2]

Our study had certain limitations. The number of infants reintubated in the first 48 hours after extubation was relatively small when compared with the total number of infants reintubated, as reflected by the wider 95% CIs observed as the time to reintubation was shortened. This suggests a greater degree of uncertainty with regards to the true strength of the association, and compels for larger studies to validate our results. Because of the small number of deaths, we only evaluated the effects of mortality as part of a composite outcome rather than a separate entity. Although we adjusted for several important variables known to increase death or BPD, it is possible that other confounders may have been unaccounted for. Because we only evaluated the impact of reintubations after the first elective extubation, our results may not apply to reintubations that occurred after previously failed extubation attempt(s) or after an accidental extubation.

In conclusion, results from our exploratory analysis indicate that although reintubations appear to be independently associated with an increased risk of death/BPD in extremely preterm infants, this significance is predominantly attributed to infants reintubated within ≤48 hours from extubation. Furthermore, our findings validate prior concerns that the cumulative duration of mechanical ventilation plays an important confounding role in the increased risk of death/BPD and BPD perceived with some reintubations. Thus, future research aimed at developing prediction models of extubation success should target the identification of reintubations that occur in the first 48 hours following extubation. In the meantime, given the absence of predictors capable of accurately identifying this high-risk minority, infants should be extubated as early as deemed possible to mitigate the known risks associated with prolonged mechanical ventilation exposure. ■

Submitted for publication May 31, 2018; last revision received Aug 14, 2018; accepted Sep 24, 2018

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References

1. Shalish W, Kanbar L, Keszler M, Chawla S, Kovacs L, Rao S, et al. Patterns of reintubation in extremely preterm infants: a longitudinal cohort study. Pediatr Res 2018;83:969-75.

2. Jensen EA, DeMauro SB, Kornhauser M, Aghai ZH, Greenspan JS, Dysart KC. Effects of multiple ventilation courses and duration of mechanical ventilation on respiratory outcomes in extremely low-birth-weight infants. JAMA Pediatr 2015;169:1011-7.
3. Kirpalani H, Millar D, Lemyre B, Yoder BA, Chiu A, Roberts RS, et al. A trial comparing noninvasive ventilation strategies in preterm infants. New Engl J Med 2013;369:611-20.
4. Choi YB, Lee J, Park J, Jun YH. Impact of prolonged mechanical ventilation in very low birth weight infants: results from a National Cohort Study. J Pediatr 2018;194:34-9.
5. Walsh MC, Morris BH, Wrage LA, Vohr BR, Poole WK, Tyson JE, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. J Pediatr 2005;146:798-804.
6. Manley BJ, Doyle LW, Owen LS, Davis PG. Extubating extremely preterm infants: predictors of success and outcomes following failure. J Pediatr 2016;173:45-9.
7. Chawla S, Natarajan G, Shankaran S, Carper B, Brion LP, Keszler M, et al. Markers of successful extubation in extremely preterm infants, and morbidity after failed extubation. J Pediatr 2017;189:113-9.
8. Thille AW, Richard JC, Brochard L. The decision to extubate in the intensive care unit. Am J Respir Crit Care Med 2013;187:1294-302.
9. Epstein SK, Ciubotaru RL. Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation. Am J Respir Crit Care Med 1998;158:489-93.
10. Tobin MJ. Extubation and the myth of "minimal ventilator settings". Am J Respir Crit Care Med 2012;185:349-50.
11. Shalish W, Kanbar LJ, Rao S, Robles-Rubio CA, Kovacs L, Chawla S, et al. Prediction of Extubation readiness in extremely preterm infants by the automated analysis of cardiorespiratory behavior: study protocol. BMC Pediatr 2017;17:167.
12. Kanbar LJ, Shalish W, Precup D, Brown K, Sant'Anna GM, Kearney RE. eds. Automated ongoing data validation and quality control of multi-institutional studies. In: Conference of the proceedings IEEE engineering medicine biology society. 2016. p. 2504-7.
13. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163:1723-9.
14. Kramer MS, Platt RW, Wen SW, Joseph KS, Allen A, Abrahamowicz M, et al. A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics 2001;108:E35.
15. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978;187:1-7.
16. Cabello B, Thille AW, Roche-Campo F, Brochard L, Gomez FJ, Mancebo J. Physiological comparison of three spontaneous breathing trials in difficult-to-wean patients. Intensive Care Med 2010;36:1171-9.
17. Sassoon CS, Light RW, Lodia R, Sieck GC, Mahutte CK. Pressure-time product during continuous positive airway pressure, pressure support ventilation, and T-piece during weaning from mechanical ventilation. Am Rev Respir Dis 1991;143:469-75.
18. Lemaire F, Teboul JL, Cinotti L, Giotto G, Abrouk F, Steg G, et al. Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. Anesthesiology 1988;69:171-9.
19. Straus C, Louis B, Isabey D, Lemaire F, Harf A, Brochard L. Contribution of the endotracheal tube and the upper airway to breathing workload. Am J Respir Crit Care Med 1998;157:23-30.
20. Hatch LD, Grubb PH, Lea AS, Walsh WF, Markham MH, Whitney GM, et al. Endotracheal intubation in neonates: a prospective study of adverse safety events in 162 infants. J Pediatr 2016;168:62-6.
21. Foglia EE, Ades A, Napolitano N, Leffelman J, Nadkarni V, Nishisaki A. Factors associated with adverse events during tracheal intubation in the NICU. Neonatology 2015;108:23-9.

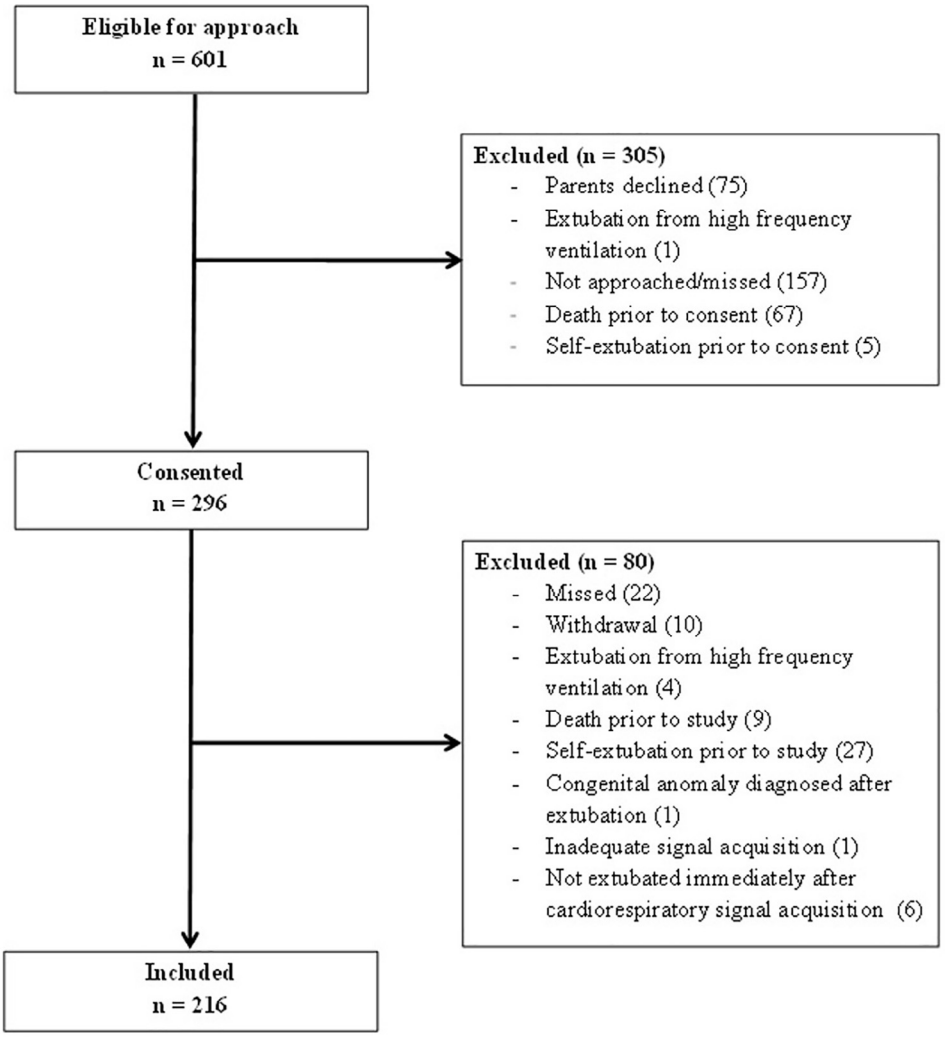

Figure 1. Flow of participants.

Table III. aOR of death/BPD and BPD among survivors for all variables included in the multivariate models

Independent variables	Multivariate model 1	Multivariate model 2
Death/BPD		
Need for reintubation*	3.07 (1.29-7.26)	2.37 (0.94-5.98)
Cumulative mechanical ventilation d	n/a	1.08 (1.03-1.13)
Birth weight	0.996 (0.994-0.999)	0.999 (0.996-1.001)
Postnatal steroids	7.23 (2.57-20.29)	2.86 (0.91-8.98)
Necrotizing enterocolitis	5.56 (1.14-27.09)	6.46 (1.21-34.58)
Postnatal infection	2.14 (0.89-5.14)	1.90 (0.77-4.72)
Study site		
Interaction term (*P* value)†	n/a	0.14
BPD among survivors		
Need for reintubation*	2.09 (0.85-5.16)	1.09 (0.38-3.15)
Cumulative mechanical ventilation d	n/a	1.13 (1.06-1.21)
Birth weight	0.996 (0.993-0.998)	0.999 (0.996-1.002)
Postnatal steroids	10.19 (3.20-32.50)	2.74 (0.74-10.08)
Necrotizing enterocolitis	6.40 (1.16-35.42)	7.01 (0.92-53.36)
Postnatal infection	2.77 (1.10-6.97)	2.69 (0.99-7.30)
Study site		
Interaction term (*P* value)†	n/a	0.50

Results are expressed as OR (95% CI) and models were adjusted for birth weight-site-postnatal infection-postnatal steroid and necrotizing enterocolitis. Model 2 was additionally adjusted for total mechanical ventilation days.
*Need for reintubation any time after the first elective extubation.
†Interaction term between need for reintubation and cumulative mechanical ventilation days. The interaction terms were not included in the multivariate model since *P* value was greater than .05.

Table V. Characteristics of infants reintubated within 48 hours vs those reintubated at 49 hours-7 days after extubation

Variables	Reintubated within 48 h (n = 28)	Reintubated at 49 h-7 d (n = 33)	*P* value
Demographics			
Gestational age, wk	25.4 [24.4-26.5]	25.4 [24.8-26.1]	.84
Birth weight, g	745 [625-854]	760 [678-885]	.46
Male sex	12 (43)	21 (64)	.10
Small for gestational age	5 (18)	5 (15)	.78
Antenatal steroids	24 (86)	31 (94)	.28
Apgar score 5 min*	8 [6-8]	6 [5-8]	.19
Cord pH†	7.29 [7.26-7.33]	7.29 [7.22-7.35]	.57
Intubation in delivery room	17 (61)	22 (67)	.63
Surfactant	28 (100)	31 (94)	.19
Caffeine	27 (96)	33 (100)	.27
Pre-extubation			
Postmenstrual age, wk	27.4 [26.5-28.4]	26.9 [26.3-27.8]	.52
Weight, g	820 [690-950]	820 [718-953]	.85
mechanical ventilation d	11 [2-25]	6 [4-18]	.97
pH§	7.31 [7.28-7.36]	7.34 [7.30-7.37]	.23
pCO2, mm Hg‡	46 [38-57]	44 [37-54]	.55
Mean airway pressure, cm H_2O	8 [6.5-9.4]	7.2 [6.5-8.3]	.29
Fraction of inspired oxygen	0.26 [0.22-0.32]	0.25 [0.23-0.27]	.21
Hemoglobin (≤24 h), g/L§	137 [126-148]	128 [125-137]	.24
Patent ductus arteriosus	11 (39)	16 (48)	.47
Intraventricular hemorrhage	7 (25)	11 (33)	.48
Necrotizing enterocolitis	2 (7)	0 (0)	.12
Postnatal steroids	8 (29)	8 (24)	.70
Postnatal infection	5 (18)	5 (15)	.78

Values are expressed as medians [IQR] or n (%).
*Data available for 27 infants reintubated within 48 hours.
†Data available for 23 infants reintubated within 48 hours and 32 reintubated between 49 hours and 7 days.
‡Data available for 26 infants reintubated within 48h and 32 reintubated between 49h-7d.
§Data available for 15 infants reintubated within 48h and 17 reintubated between 49h-7d.

Table IV. Characteristics of infant deaths

Cases	Gestational age (wk)	Birth weight (g)	DOL at extubation	Time to reintubation	DOL at death	Cause of death
Infants reintubated						
1	26.1	980	2	0.5 h	2	Pulmonary hemorrhage
2	26.1	950	2	7 h	5	Grade 4 IVH*
3	26.6	890	18	8 h	20	NEC
4	25.4	710	27	51 h	74	Gram negative sepsis
5	31.7	760	2	88 h	6	NEC
6	26.7	870	5	6 d	17	Pulmonary hemorrhage
7	28.7	1090	4	15 d	19	NEC and gram negative sepsis
8	27.4	700	5	24 d	98	Chronic hypoxia*
9	27.4	1050	4	46 d	56	Midgut volvulus
Infant never reintubated						
10	25.1	510	68	N/A	170	Pulmonary hypertension, BPD*

DOL, day of life; *IVH*, intraventricular hemorrhage; *NEC*, necrotizing enterocolitis.
*Withdrawal of life-sustaining therapy.