

JOHNS HOPKINS ALL CHILDREN'S HOSPITAL

# Invasive Ventilation Strategies and Extubation Readiness for Premature Neonates Clinical Practice Guideline

# Invasive Ventilation Strategies and Extubation Readiness Premature Neonates

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# Invasive Ventilation Strategies and Extubation Readiness for Premature Neonates

Johns Hopkins All Children's Hospital

## Rationale

- A. To provide guidance on evidence-based strategies for invasive mechanical ventilation in neonates born < 37 weeks gestation.
- B. To provide general guidance on respiratory parameters warranting ventilator weaning stratified by chronologic age.
- C. To provide respiratory and clinical parameters at which extubation should be attempted in mechanically ventilated infants

## Background

Mechanical ventilation (MV) remains an important supportive measure for newborns with respiratory distress. It often provides critical support for term infants with respiratory failure and younger and more premature infants born before 28 weeks of gestation. Although potentially life-saving, invasive MV has is associated with some unfavorable outcomes on the cardiovascular system, brain and lungs which have been demonstrated in various studies. Given this potential for morbidity associated with MV, it is important to use strategies that minimize the possible negative impact of prolonged MV with the goal to provide gentle ventilation and extubation as early and safely as possible.

## Published Data and Levels of Evidence

### Goals of Mechanical Ventilation in Premature Neonates

1. Maintenance of adequate, not necessarily normal, gas exchange with as minimal lung injury as possible and with the least degree of hemodynamic impairment.
2. Minimizing ventilator-associated lung injury (VALI) by utilizing adequate inflation volumes to avoid *volutrauma* (lung injury caused by overdistention and excessive stretch of tissues which leads to disruption of alveolar and small airway epithelium resulting in edema) as well as *atelectrauma* (lung damage caused by tidal ventilation in the presence of atelectasis leading to maldistribution of tidal volume and regional volutrauma).

### Impacts of Invasive Mechanical Ventilation on Neonatal Outcomes

More prolonged mechanical ventilation has been shown in a number of observational studies to be associated with adverse neonatal and later neurodevelopmental outcomes. In a study of 5364 infants with a birthweight of 501-1000 g born at National Institute of Child Health and Human Development (NICHD) Neonatal Research Network centers, each week of additional MV was associated with a significant increase in the likelihood of neurodevelopment impairment (Walsh, 2005). In a prospective Canadian cohort study of 144 neonates born before 30 weeks gestation, Guillot et al. demonstrated the impact of each additional day of MV on impaired brainstem development, abnormal white matter maturation, and lower motor scores at preschool age (Guillot, 2020). In a large multicenter United States cohort of infants born at or below 28 weeks of gestation, mechanical ventilation at 36 weeks PMA was associated with a six-fold increase in quadriparetic cerebral palsy (Van Marter, 2011). In a large Korean cohort study of 69 NICUs evaluating 3508 very low birth weight infants, the adjusted hazard ratio for the primary outcome of death increased significantly in infants receiving MV for more than 2 weeks compared to those receiving MV for less than 7 days. Additionally, the cumulative duration of MV was associated with increased odds of bronchopulmonary dysplasia (BPD), pulmonary hypertension, surgical retinopathy of prematurity (ROP), periventricular leukomalacia (PVL), and abnormal auditory screening tests (Choi, 2017). In another large cohort study of 11,806 infants <28 weeks gestation admitted to a NICU in England, MV for >8 days predicted BPD development with 71% sensitivity and 71% specificity and MV for >10 days predicted discharge on home oxygen with 66% sensitivity and 65% specificity (Dassios, 2021).

Since sicker babies are likely to require more prolonged ventilation, it is impossible to make inferences using observational data whether the relationship between adverse outcomes and prolonged ventilation is causal or represents confounding by indication. Nevertheless, laboratory data suggest that, compared with CPAP, mechanical ventilation is associated with lung injury and inflammation.

## Modes of Ventilation: Volume-Targeted Ventilation (VTV) vs. Pressure Limited Ventilation (PLV)

Pressure Limited Ventilation (PLV) has historically been the primary mode for ventilating preterm infants and now has been shown to be inferior in reducing lung injury to other forms of mechanical ventilation such as volume targeted ventilation, high frequency oscillatory ventilation and continuous positive airway pressure (CPAP).

In PLV, an operator-set Peak Inspiratory Pressure (PIP) is entered to be delivered at a specific time interval. The derived tidal volume (Vt) is determined by the set pressure and the lung compliance of the patient, and therefore can be variable depending on the dynamic component of lung compliance.

Volume-Targeted Ventilation (VTV) aims to deliver a consistent Vt and is recognized as an effective and advantageous method for providing mechanical ventilation to preterm infants. An operator set Vt is entered to be delivered at specific time interval, and a maximum PIP limit is set. The ventilator will adjust the PIP up or down within a prescribed pressure limit to achieve the Vt target. Thus, the PIP will vary in response to changing lung compliance to provide the set Vt.

A Cochrane systematic review and meta-analysis evaluating 16 parallel trials (977 infants) and four cross-over trials (88 infants) compared VTV with PLV in neonates and found no difference in death before hospital discharge (low quality evidence). However, there was moderate quality evidence that the use of VTV modes resulted in a reduction in death or BPD at 36 weeks gestation, pneumothorax, mean days of mechanical ventilation, rates of hypocarbia, grade 3 or 4 intraventricular hemorrhage, and the combined outcome of periventricular leukomalacia with or without grade 3 or 4 intraventricular hemorrhage as demonstrated in the table below (Klingenberg, 2017). Although findings in the review appear to favor the use of VTV, the authors caution for careful education in units considering VTV and advise for the need for further study of different volume targeting strategies.

<b>Outcomes</b>	<b>Relative Risk or Mean Difference</b>	<b>95% CI</b>	<b>No. of participant (studies)</b>	<b>Quality of Evidence (GRADE)</b>
Death before discharge from hospital	0.75	0.53-1.07	771 (11 RCTs)	Low
<i>Death or BPD (at 36 wks)</i>	<i>0.73</i>	<i>0.59-0.89</i>	<i>584 (8 RCTs)</i>	<i>Moderate</i>
Days on Mechanical Ventilation	-1.35		736 (12 RCTs)	Moderate
Pneumothorax	0.52	0.31-0.87	825 (13 RCTs)	Moderate
<i>IVH Grade 3-4</i>	<i>0.53</i>	<i>0.37-0.77</i>	<i>712 (10 RCTs)</i>	<i>Moderate</i>
<i>PVLM ± IVH Grade 3-4</i>	<i>0.47</i>	<i>0.27-0.80</i>	<i>441 (6 RCTs)</i>	<i>Moderate</i>

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There are some barriers and associated hesitations to adopting VTV, including lack of suitable ventilators to ensure accurate delivery of set Vt, presence of endotracheal tube (ETT) leak, and lack of clarity of optimal Vt for each patient (Keszler, 2019).

Ensuring the accuracy of the delivered Vt is of particular concern in extremely low birth weight (ELBW) infants. Measurements obtained at the patient end rather than at the ventilator end of the circuit are thought to increase accuracy as it is not subject to the compressible gas volume and compliance of the ventilator circuit. A prospective cohort study examining the tidal volume variation when using a volume-targeted mode and a proximal flow sensor showed good correlation of measured expired Vt between very low birth weight (VLBW) and ELBW infants (Wong, 2019).

Endotracheal tube air leaks are common in intubated preterm infants and can present a particular challenge when providing VTV. A regression analysis in a retrospective study indicated Vt was underestimated by 1.2 ml/kg in the presence of a tracheal tube leak of >40% (Mahmoud, 2011). Additionally, a retrospective analysis of 30 ventilatory recordings demonstrated declining expiratory tidal volume with ETT leaks >50% when leak compensation was not used. When leak compensation was used, expired Vt was well maintained with ETT leaks >90%, although with large variability (Szakmar, 2018). It is recommended that if a patient is unable to be extubated due to continued need for MV support, the ETT size be exchanged to a larger size to allow for decreased leak.

Because of its built-in compensatory mechanisms for leak and accuracy of measuring tidal volume delivered, the Dräger® is the preferred ventilator for volume-targeted ventilation.

The ideal Vt for each patient is variable and depends on the infant's size, postnatal age, and underlying disease process. Below is a table with recommended Vt and PIP settings for different clinical situations and patient conditions (Keszler, 2019). Large Vt are needed in the smaller infants due to a larger impact of dead space which ranges 0.7-1.1mL depending on the device. Additionally, older infants with evolving BPD need a larger Vt to account for anatomic and alveolar dead space which is inherent to the disease pathology.

<b>Condition</b>	<b>Initial Vt with rationale</b>	<b>Initial PIP limit with rationale</b>	<b>Reference</b>
Term, late preterm, normal lungs	4-4.5mL/kg Baseline	18cm H2O Normal compliance	Dawson, 2005
Preterm RDS 1250-2500g	4-4.5mL/kg Low alveolar dead space	26cm H2O Decreased compliance	Dawson, 2005
Preterm RDS 700-1249g	4.5-5mL/kg Dead space of flow sensor	24cm H2O Decreased compliance, risk of air leak	Nassabeh-Montazami, 2009
Preterm RDS <700g	5.5-6mL/kg Dead space of the flow sensor	24cm H2O Decreased compliance, risk of air leak	Nassabeh-Montazami, 2009
Preterm evolving BPD 3 weeks old	5.5-6.5mL/kg Increased anatomical and alveolar dead space	26 cm H2O Worsening compliance	Keszler, 2009

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## Modes of Mechanical ventilation: High frequency oscillatory ventilation (HFOV) vs. Conventional Mechanical Ventilation (CMV)

HFOV is a ventilation strategy that uses a constant distending pressure (Mean Airway Pressure-MAP) with pressure variations that oscillate around the MAP at high rates. A Cochrane systematic review and meta-analysis that included 19 studies and 4096 participants compared elective HFOV to CMV in preterm infants (Cools, 2015). There was a small reduction in the risk of chronic lung disease (at 36 weeks) when elective HFOV was used compared to CMV, however there was inconsistency of this effect across all trials. Findings from the meta-analysis are presented below. The authors mention the need for further research to identify specific populations that may benefit from early HFOV, comparison of HFOV to CMV after early failure of non-invasive (NIV), evaluation of effects of different devices used to generate HFOV, and long-term growth and development of patients treated with HFOV versus CMV. Of note, the CMV modes analyzed in this review were very heterogenous, with only 5/19 of the studies utilizing VTV. There have not been any metanalyses comparing HFOV to VTV directly.

<b>Primary Outcomes</b>	<b>Risk Ratios</b>	<b>95% CI</b>	<b>No. of participants (studies)</b>	<b>Favors</b>
Mortality at 28 to 30 days	1.09	0.88-1.34	2148 (10 RCTs)	Neither
Mortality at by 36 to 37 weeks PMA	0.95	0.81-1.10	3329 (17 RCTs)	Neither
CLD: O <sub>2</sub> at 28 to 30 days	0.98	0.88-1.10	1043 (6 RCTs)	Neither
CLD O <sub>2</sub> or PPV at 36 to 37 weeks PMA	0.86	0.78-0.96	2786 (17 RCTs)	HFOV
Death or CLD at 36 weeks PMA	0.94	0.85-1.04	1160 (5 RCTs)	Neither
<b>Secondary Outcomes</b>				
Pulmonary air leak including PIE	1.19	1.05-1.34	2854 (13 RCTs)	CMV
IVH: All Grades	1.04	0.95-1.14	3084 (12 RCTs)	Neither
IVH: Grades 3 or 4	1.1	0.95-1.27	4069 (18 RCTs)	Neither
PVLM	1.03	0.81-1.31	3983 (17 RCTs)	Neither
ROP ( $\geq$ stage 2)	0.81	0.7-0.93	2781 (12 RCTs)	HFOV

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Literature on acceptable parameters for extubation and extubation readiness in neonates

There is no discrete literature related to extubation criteria for neonates. There are some studies refuting the use of CPAP-pressure support trials as it relates to assessment of “extubation readiness” in intubated preterm infants (Shalish, 2019). There have been a few small-scale studies that have attempted to develop prediction models for extubation success using clinical variables of weight, gestational age, FiO2 requirement in the first 24 hours, lower pre-extubation oxygen needs, MAP and pCO2, pre-extubation pH (Gupta, 2019).

In a publication from the pediatric mechanical ventilation consensus conference (PEMVECC) which aimed to provide evidence-based recommendations on ventilation modalities, monitoring, targets of oxygenation and ventilation, supportive measures, and weaning and extubation readiness, the group determined that “There are insufficient data to recommend on the timing of initiation (strong agreement) and approach to weaning (strong agreement) and the routine use of any extubation readiness testing that is superior to clinical judgement (strong agreement)” (Kneyber, 2017).

Various randomized-controlled clinical trials related to the management of RDS in premature infants have been performed, each with specific extubation criteria used for their populations. Below is a table outlining these studies’ extubation parameters.

Study	Gestational ages	Extubation timeframe	pH	pCO2	FiO2	MAP (cmH2O)	Other
SUPPORT (NICHD, 2010)	24-27 weeks	Within first 14 DOL	≥7.30	≤50	≤35%	≤8	RR 20 or Amp<2xMAP Hemodynamically stable without evidence of clinically significant PDA
CURPAP (Lista, 2015)	25-28 weeks	After loading dose of caffeine	>7.20	<65	<40%	≤7	Hemodynamically stable without evidence of clinically significant PDA
VON-DRM (Dunn, 2011)	26-29 weeks	Stability for 6 hours	N/A	N/A	≤30%	≤8	As clinically indicated by provider

In a systematic review of published definitions of extubation success in very preterm infants <32 weeks, the authors found a wide range of variability in defining the duration of extubation success, reported extubation criteria, and reintubation criteria. The most common criteria used for extubation criteria were PIP, FiO2, and mechanical ventilation rate—although the ranges for each were large. Below is a table depicting the factors for extubation criteria, the number of publications utilizing each factor, and the median/ranges for each factor.

Extubation Criteria (N=21)	N studies utilizing criteria (%)	Median (range)
FiO2	16 (76)	35 (25-40)
PIP	15 (71)	16 (12-20)
Ventilator rate	15 (71)	20 (12-35)
PaCO2	5 (24)	60 (45-65)
PEEP	4 (19)	4 (3-5)
MAP	4 (19)	8.5 (5-10)
pH	3 (14)	7.25
Amplitude	2 (10)	20
Frequency	1 (5)	9
PaO2	1 (5)	50
Hb	1 (5)	13
Minute ventilation test	2 (10)	Pass
Spontaneous breathing trial	1 (5)	Pass

Failing to recognize an infant's potential for extubation exposes them to unnecessary time receiving MV while premature extubation increases the risk of clinical instability and reintubation. With the knowledge that there is not scientific basis for determining extubation readiness, the decision relies on the clinicians clinical acumen, experience, and personal preference. In a review of the available knowledge on extubation success in neonates, Shalish et al. provide suggestions on how to streamline and improve extubation readiness in extremely preterm infants undergoing their first planned extubation during the first 4 weeks of life are listed in the table below (Shalish, 2022).

Recommendations for weaning and assessment of extubation readiness in clinical practice
1. Routine and proactive assessment of extubation potential: <ul style="list-style-type: none"> <li>a. Discuss as a multidisciplinary team during rounds</li> <li>b. Infants should not be kept intubated solely based on age or weight</li> </ul>
2. Strategies to expedite weaning and reduce mechanical ventilation duration: <ul style="list-style-type: none"> <li>a. Optimize nutrition and fluid management</li> <li>b. Optimize caffeine maintenance dose in cases of inconsistent respiratory drive</li> <li>c. Consider postnatal steroids</li> <li>d. Wean or cease sedation</li> <li>e. Develop and implement respiratory therapist and/or nursing-driven weaning protocols</li> </ul>
3. Parameters to consider extubation (at any time point during the day or night) on conventional or high frequency oscillatory ventilation: <ul style="list-style-type: none"> <li>a. Mean airway pressure: 6-8 cm H2O</li> <li>b. FiO2 21-30%</li> <li>c. Peak inflation pressure (preset on pressure-controlled ventilation or achieved during volume-controlled ventilation): 12-15 cm H2O</li> <li>d. pH prior to extubation 7.3-7.4</li> </ul>
4. Spontaneous breathing trials or any other extubation readiness trials are not advised

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## Clinical Management

### A. Recommendation for CMV in Premature Infants:

1. Initial mode of ventilation for all patients: Volume-targeted ventilation
  - a. Dräger® ventilator
  - b. If Dräger® unavailable, acceptable alternative ventilator using proximal flow sensor
  
2. Suggested initial settings:
  - a. Mode: Volume-targeted ventilation— either SIMV with Pressure Support \* or Assist Control acceptable
  - b. Tidal volume:

Condition	Starting Vt with rationale
Term, late preterm, normal lungs	4-4.5mL/kg Baseline
Preterm RDS 1250-2500g	4-4.5mL/kg Low alveolar dead space
Preterm RDS 700-1249g	4.5-5mL/kg Dead space of flow sensor
Preterm RDS <700g	5-6mL/kg Dead space of the flow sensor
Preterm evolving BPD 3 weeks old	5.5-6.5mL/kg Increased anatomical and alveolar dead space

- c. Rate: 40-60 BPM
    - d. PEEP: 5-6cm H<sub>2</sub>O
      - i. \* Pressure support: Goal to achieve approximately 75% but no higher than 100% of Vt of VG breaths. To accomplish this, the operator should adjust it so the PS such that the PIP does not exceed that of the volume-targeted breath
    - e. Inspiratory time: 0.3-0.35 seconds
  
3. Ventilator should be adjusted according to following factors:
  - a. Clinical exam:
    - i. Tachypnea, deep retractions
      1. Assess for pathologic underlying reasons (pneumothorax, metabolic acidosis, etc.)
      2. Increase ventilator support
  - b. Chest X-ray inflation: adjust settings for optimal inflation
  - c. Patient ventilator interactions:
    - i. Very low PIPs on volume-targeted breaths may indicate need for increased support. If patient displays increased WOB or oxygen requirement, respond by increasing support with increase Vt

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- ii. Very low PIPs on volume targeted breaths without increased WOB or oxygen requirement, consider extubation
- iii. PIP or Vt during pressure-supported breaths should not exceed PIP or Vt during volume-targeted breaths. If using SIMV with PS, PS should be set to achieve 75-100% of the set Vt during pressure supported breaths
- iv. An increased Vt observed with pressure-supported breaths may suggest improved compliance and ability to wean ventilator
- d. Blood gas monitoring with goal PCO<sub>2</sub> 45 – 55 (Week 1), 55-65 (>week 1)
- e. Oxygenation. Goal O<sub>2</sub> saturation 90-95% with the least amount of oxygen supplementation, and assessment of histogram each shift

## B. Limitations:

### a. Leak:

- a. Mechanical issues (flow sensor malfunction, ventilator circuit compromise)
- b. Patient positioning
- c. Consider Dräger if patient on different ventilator
- d. If patient achieving adequate ventilation and oxygenation despite significant leak, trial of extubation
- e. Upsize ETT if patient not stable for extubation
- f. Only if all of the above have been addressed and the leak continues to be significant with alarm, consider conversion to pressure-limited ventilation

### b. Considerations for use of high frequency ventilation:

- a. Pulmonary hypoplasia, PIE, air-leak syndromes
- b. Failure to adequately support ventilation and oxygenation in patient with maximal ventilator settings on Volume-targeted ventilation:
  - i. Volume: 6mL/kg
  - ii. RR: 60
  - iii. PEEP: 6cm H<sub>2</sub>O
  - iv. Persistent PCO<sub>2</sub> > 60 for >2 blood gases within the first week of life
  - v. FiO<sub>2</sub> >60% without improvement

## Recommendation for parameters for weaning and “Extubation Readiness”

Extubation should be considered if a patient meets the following criteria:

Parameter	<7 days	7-14 days
FiO2	≤ 35%	≤ 40%
PCO2	≤55	≤60
TV	≤6mL/kg	≤6mL/kg
CMV MAP (average)	≤10	≤10
HFOV MAP	≤12	≤12
Other	<ul style="list-style-type: none"><li>• Recommend weaning off sedative medications prior to extubation</li><li>• Patient must have sufficient respiratory effort</li><li>• Frequent desaturations on MV should not be a contraindication to extubation, as many times hypoxemia results from loss of FRC associated with abdominal contractions and not related to lung disease (Bancalari, 2018)</li><li>• Consider pretreating with caffeine</li></ul>	

Once patient meets extubation criteria, refer to “Guidelines for Non-Invasive Respiratory Support for Patients Status Post RDS and evolving BPD” for guidance on settings for non-invasive ventilation, and criteria for failed extubation.

### Summary

- The literature supports the use of volume-targeted ventilation as the initial mode of invasive conventional ventilation in premature infants
- There are no specific parameters in the literature that determine “extubation readiness” in premature infants, but efforts should be made to extubate as early and safely as possible to avoid morbidities associated with prolonged mechanical ventilation

### Glossary

VALI: Ventilator-associated lung injury  
MV: Mechanical ventilation  
BPD: Bronchopulmonary dysplasia  
ROP: Retinopathy of prematurity  
PVLM: Periventricular leukomalacia  
CPAP: Continuous positive airway pressure  
VTV: Volume-targeted ventilation  
PLV: Pressure-limited ventilation  
Vt: Tidal volume  
PIP: Peak inspiratory pressure  
ETT: Endotracheal tube

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ELBW: Extremely low birth weight  
VLBW: Very low birth weight  
RDS: Respiratory distress syndrome  
HFOV: High frequency oscillatory ventilation  
MAP: Mean airway pressure  
NIV: Non-invasive ventilation  
CMV: Conventional mechanical ventilation  
CLD: Chronic lung disease  
IVH: Intraventricular hemorrhage  
PMA: Postmenstrual age  
RCT: Randomized controlled trial  
PIE: Pulmonary interstitial emphysema  
FiO<sub>2</sub>: fraction of inspired oxygen  
PEEP: Positive end expiratory pressure  
Hb: Hemoglobin  
BPM: Breaths per minute  
PS: Pressure support

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