



# A narrative review of advanced ventilator modes in the pediatric intensive care unit

Andrew G. Miller<sup>1,2</sup>, Renee M. Bartle<sup>1,2</sup>, Alexandra Feldman<sup>1,3</sup>, Palen Mallory<sup>1,3</sup>, Edith Reyes<sup>1,3</sup>, Briana Scott<sup>1,3</sup>, Alexandre T. Rotta<sup>1,3</sup>

<sup>1</sup>Duke University Medical Center, Durham, NC, USA; <sup>2</sup>Respiratory Care Services, Duke University Medical Center, Durham, NC, USA; <sup>3</sup>Division of Pediatric Critical Care Medicine, Duke University Medical Center, Durham, NC, USA

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*Correspondence to:* Andrew G. Miller, MSc, RRT-ACCS, RRT-NPS. Duke University Medical Center, Respiratory Care Services, 2301 Erwin Rd, Durham, NC 27710, USA. Email: Andrew.g.miller@duke.edu.

**Abstract:** Respiratory failure is a common reason for pediatric intensive care unit admission. The vast majority of children requiring mechanical ventilation can be supported with conventional mechanical ventilation (CMV) but certain cases with refractory hypoxemia or hypercapnia may require more advanced modes of ventilation. This paper discusses what we have learned about the use of advanced ventilator modes [e.g., high-frequency oscillatory ventilation (HFOV), high-frequency percussive ventilation (HFPV), high-frequency jet ventilation (HFJV) airway pressure release ventilation (APRV), and neurally adjusted ventilatory assist (NAVA)] from clinical, animal, and bench studies. The evidence supporting advanced ventilator modes is weak and consists of largely of single center case series, although a few RCTs have been performed. Animal and bench models illustrate the complexities of different modes and the challenges of applying these clinically. Some modes are proprietary to certain ventilators, are expensive, or may only be available at well-resourced centers. Future efforts should include large, multicenter observational, interventional, or adaptive design trials of different rescue modes (e.g., PROSpect trial), evaluate their use during ECMO, and should incorporate assessments through volumetric capnography, electric impedance tomography, and transpulmonary pressure measurements, along with precise reporting of ventilator parameters and physiologic variables.

**Keywords:** High-frequency ventilation; mechanical ventilation; pediatric; airway-pressure release ventilation; neurally adjusted ventilatory assist (NAVA)

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## Introduction

Respiratory failure is a common reason for pediatric intensive care unit (PICU) admission. The vast majority of children requiring mechanical ventilation can be supported with conventional mechanical ventilation (CMV) but certain cases with refractory hypoxemia or hypercapnia may require more advanced modes of ventilation; although high-level evidence supporting these modes is limited. For

the purposes of this review, advanced ventilator modes include high-frequency oscillatory ventilation (HFOV), high-frequency percussive ventilation (HFPV), high-frequency jet ventilation (HFJV) airway pressure release ventilation (APRV), and neurally adjusted ventilatory assist (NAVA). Adaptive Support Ventilation was considered for inclusion; however, we determined the mode was an advanced servo regulated mode similar to pressure-regulated pressure control. Proportional assist ventilation

(PAV+) was also considered for inclusion but we were unable to identify any studies germane to the PICU; PAV+ has been found to be feasible and safe in premature neonates (1). We present the following narrative review in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/tp-20-332>) on the use of advanced ventilator modes in pediatric critical care and discuss evidence generated from clinical, animal, and bench studies.

## Methods

We searched MEDLINE for studies done in pediatric patients for clinical studies and all bench and animal studies potentially relevant to pediatric critical care, excluding studies of neonates or premature animal models. Adult animal and bench models were included as they are applicable to older children. All studies published prior to October 1, 2020 were included unless specifically stated in the individual sections. Searches were supplemented by reviewing references within individual papers. We reviewed primary sources for pediatric studies and relied on systematic reviews of adult data. The keywords used for the search included: high-frequency ventilation, HFOV, HFPV, HFJV, airway-pressure release ventilation, and NAVA. Boolean logic was used to limit the search to children and identify animal studies.

## Principles and physiology of high-frequency ventilation

During normal spontaneous breathing and CMV, gas movement occurs due to convection and molecular diffusion. Convection is the bulk flow of gas through the conducting airways [anatomical dead space (VD)] as the result of a pressure gradient caused by diaphragm contraction during normal breathing or from positive pressure ventilation. Diffusion is the movement of gas molecules down a concentration gradient in the distal parts of the airway and alveoli. Based on these mechanisms, alveolar ventilation (VA) theoretically can only occur if the tidal volume (VT) exceeds VD.

High-frequency ventilation uses a VT that often is lower than VD but alveolar ventilation still occurs. The precise mechanisms of gas transport during high-frequency ventilation remain unclear and vary depending on the high frequency technique employed, yet six distinct gas transport mechanisms have been proposed (*Figure 1*).

These are bulk gas flow, pendelluft, cardiogenic mixing, asymmetric velocity profiles, Taylor dispersion, and molecular diffusion (2-7). The details of gas exchange mechanisms during high-frequency ventilation is beyond the scope of this article and have been reviewed elsewhere (2-7).

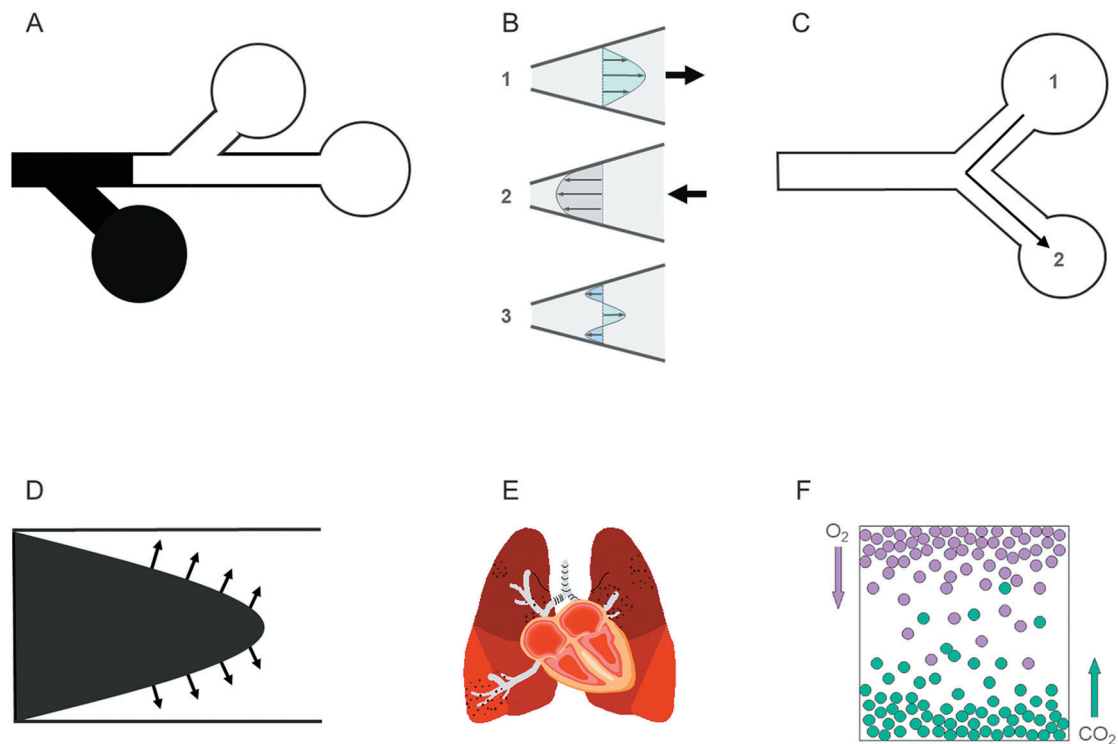
## HFOV

HFOV is a technique that employs respiratory rates between 5 and 15 Hz (300 to 900 breaths per minute), and a VT (approximately 1–3 mL/kg) that often are  $\leq$  VD. During HFOV, the ventilator circuit is pressurized by the combination of bias flow (gas entering the circuit) and leakage through a low pass filter or exhalation valve (gas leaving the circuit) that determines the mean airway pressure (mPaw). Gas is then displaced towards and away from the patient through a piston or a magnetically controlled piston-diaphragm system.

HFOV is unique in that both inspiration and exhalation are active processes. During HFOV, oxygenation and ventilation are relatively independent, although overdistension or low functional residual capacity may affect carbon dioxide (CO<sub>2</sub>) clearance. Oxygenation is controlled by the fraction of inspired oxygen (FiO<sub>2</sub>) and mPaw while ventilation is dependent on VT (amplitude, controlled by the power setting) and frequency (in Hz). Ventilation is inversely proportional to frequency; lower frequencies result in higher VT and increased ventilation. VT increases or decreases in the same direction as amplitude. Pressure amplitude in the more distal airways is significantly attenuated during HFOV, thus mechanical strain and stress on the alveoli are minimized. HFOV has been purported as a form of lung protective ventilation that minimizes volutrauma, atelectrauma, and biotrauma (8). A detailed description of HFOV physiology, gas transport mechanisms, and settings for various clinical conditions is beyond the scope of this article and has been discussed elsewhere (3,9).

## Clinical studies

HFOV has been well studied in adults with ARDS (10-16), but randomized controlled trials (RCTs) in pediatric ARDS (PARDS) are sparse. A meta-analysis performed prior to two large RCTs—OSCAR (13) and OSCILLATE (14)—concluded HFOV might improve survival and is unlikely to cause harm, but the analysis included studies where the control groups did not receive lung-protective ventilation (17). While the OSCAR



**Figure 1** Mechanisms of gas exchange during high-frequency ventilation. (A) Direct ventilation by bulk gas movement reaching the most proximal alveoli. (B) Streaming of gas flow in a diverging conduit: 1, inspiration; 2, active exhalation; 3, net effect depicting fresh gas being transported through the center of the airway and carbon dioxide-rich gas through the periphery of the airway. (C) Pendelluft between two adjacent alveoli of different time constants: a fast alveolus [1] emptying into a slow alveolus [2]. (D) Radial mixing from diffusion during augmented (Taylor) dispersion. (E) Cardiogenic mixing. (F) Molecular diffusion along concentration gradients.

trial showed no benefit of HFOV over protective CMV, the OSCILLATE trial found that HFOV increased mortality, possibly due to the inclusion of a large number of patients with sepsis and hemodynamic instability. Subsequent meta-analyses that included OSCAR and OSCILLATE did not demonstrate a survival benefit for HFOV, especially when excluding studies in which the control group did not receive lung-protective ventilation (18-20).

### *Pediatric studies*

An early report demonstrated that HFOV using a high mean lung volume strategy was safe and effective in seven children with diffuse alveolar disease and severe respiratory failure (21). HFOV was also effective as a rescue modality in a cohort of twelve children with severe respiratory failure

refractory to CMV (22). The first RCT comparing HFOV to CMV in 70 children with severe hypoxemic respiratory failure showed that HFOV improved oxygenation and decreased the need for supplemental oxygen at 30 days, but did not decrease mortality (23). Another RCT involving 61 children (HFOV =37 *vs.* CMV =24) with acute hypoxemic respiratory failure was stopped prematurely for lower than expected enrollment (11). Analysis of the available data did not demonstrate differences, but a post-hoc analysis suggested that HFOV might be beneficial in patients with an oxygenation index greater than 30 (11).

A recent retrospective observational study compared outcomes of HFOV to CMV using propensity score matching (24). This study included 9,177 patients from 98 hospitals in the Virtual PICU System database, and concluded that the application of HFOV (both early

and late) was associated with increased mortality. These findings must be taken with caution, since the propensity score matching used in that study did not include clinically important variables, such as  $\text{FiO}_2$ , airway pressures, and arterial blood gas measurements. Therefore, it is possible the subjects receiving HFOV represented a sicker cohort (24). A multicenter study of HFOV *vs.* CMV used propensity score matching to study 118 pairs of children with PARDS found HFOV was associated with increased mortality but no difference in ventilator-free days (25). In a secondary analysis of the RESTORE trial, propensity score matching found early application of HFOV was associated with longer duration of mechanical ventilation but did not affect mortality (26).

de Jager *et al.* recently described the feasibility of a physiologic, open-lung recruitment strategy of HFOV in 143 subjects treated in a single center (27). This strategy uses a starting frequency of 12 Hz for all subjects and uses incremental-decremental staircase adjustments to select the “optimal” mPaw on the deflation limb of pressure-volume curve (27). Ventilation is controlled by adjusting the frequency after maximizing the power (amplitude) setting (27). This is in contrast to prior HFOV strategies, which have used a fixed starting frequency based on the patient’s size and controlled ventilation with changes in power (amplitude). The reported mortality for different PARDS severity was similar to the mortality reported in a large, multicenter, international point prevalence study (28). Importantly, this HFOV strategy is currently being employed in the ongoing PROSpect trial.

### **Animal studies**

Relevant animal studies of HFOV were completed over two decades ago and demonstrated it to be superior to CMV for physiologic and pathobiologic outcomes (29–33). Although crucial in refining the HFOV strategies for translation into human trials, these early studies suffered from the limitation that the CMV groups did not receive lung protective ventilation with physiologic (4–8 mL/kg) VT and adequate PEEP (29). Therefore, it was not surprising that HFOV performed better than non-protective CMV. When optimal HFOV was compared against optimal CMV, both modalities performed similarly, suggesting that a lung protective approach—accomplished through either CMV or HFOV—attenuates experimental lung injury regardless of the technique employed (34,35).

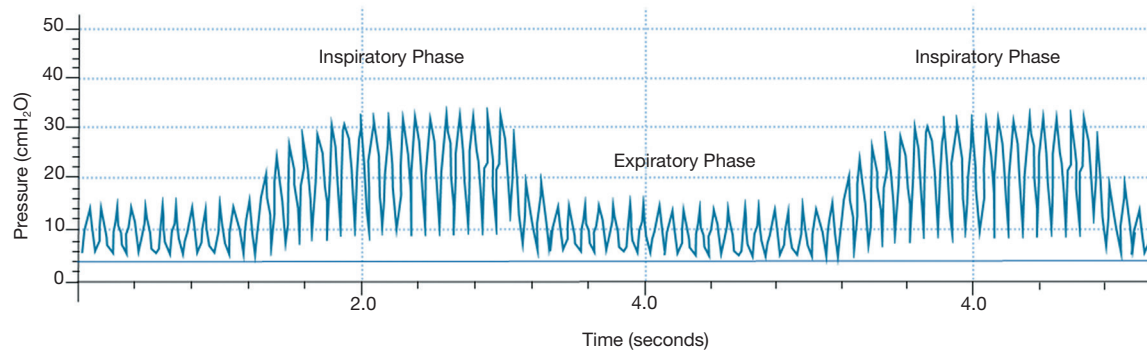
### **Conclusion and recommendations for clinical practice**

The Pediatric Acute Lung Injury Consensus Conference (PALICC) recommends that HFOV should be considered as an alternative ventilatory mode in patients with moderate-to-severe PARDS in whom plateau pressure exceeds 28 cmH<sub>2</sub>O, provided chest wall compliance is normal (36). When used, HFOV should be titrated to optimize lung volume through exploration of the potential for lung recruitment by a stepwise increase and decrease of the mPaw under continuous monitoring of the oxygenation and ventilation, along with hemodynamic parameters (36). Although the safety and feasibility of HFOV is well established in PARDS and is associated with improvement of short-term physiologic endpoints, HFOV has not been shown to improve clinically meaningful outcomes, such as mortality or ventilator-free days. HFOV is a complex, nuanced mode of ventilation with a steep learning curve, so its use must be approached with respect even by those experienced its use. Until more definitive data are available, it is reasonable to continue to utilize HFOV as an option for the management of select patients with moderate-to-severe PARDS (37).

The question of whether HFOV has a definitive role in the management of PARDS can only be answered by a large multicenter RCT. The PROSpect trial comparing HFOV to CMV and prone positioning to supine in a two-by-two factorial adaptive design is currently ongoing, with a planned enrollment of 1,000 children with acute hypoxemic respiratory failure (38).

### **HFPV**

HFPV is a pneumatically powered, time-cycled and pressure-limited ventilation form of mechanical ventilation used predominantly in inhalation injury, burns, and as a rescue mode for selected patients failing CMV. High-frequency percussive breaths are superimposed upon a conventional pressure-controlled breath, usually in a 1:1 inspiratory to expiratory ratio with 10–30 breaths per minute, depending on patient size. It can be used with other I:E ratios (39). Peak inspiratory pressure (PIP) and positive end-expiratory pressure (PEEP) are set; however, due to the Phasitron, both the PIP and PEEP “oscillate” around the set value, and the mean value for both PIP and PEEP are used (*Figure 2*). The percussive rate is set between 200 and 900 cycles per minute. Due to the unique mechanism of action, the lung is inflated in a controlled manner until the PIP is reached. Exhalation is passive and patients cannot



**Figure 2** Graphic representation of high-frequency percussive ventilation (HFPV) pressure waveforms over time. Set peak inspiratory pressure (PIP) and positive end-expiratory pressure (PEEP) are the mean values during inspiratory and expiratory phases.

trigger the ventilator, although there is a reserve volume within the circuit with which patients can spontaneously inspire gas. We reviewed the literature over the past 15 years; earlier data have been discussed elsewhere (39).

### *Clinical studies*

RCTs involving children are lacking and data are limited to case series/reports and retrospective studies (*Table 1*) (40-46). HFPV has been better studied in the adult burn population; however, case reports/series and retrospective studies comprise the majority of current data, with few RCTs and systematic reviews.

A systematic review of high frequency modalities as salvage therapy in adult and pediatric patients with smoke inhalation-associated acute lung injury concluded that HFPV may decrease mortality and pneumonia when compared to CMV, although the quality of evidence was low (47). A small before ( $n=22$ ) and after ( $n=14$ ) study found that HFPV use in pediatric extracorporeal life support (ECLS) was associated with more ECLS-free days, but not with improved survival or ventilator free days (48).

### *Animal studies*

HFPV was evaluated against large VT CMV (10 mL/kg) in a sheep burn/ARDS model and was found to increase survival without adverse hemodynamic effects (49). There were no differences in P/F ratio, although PaCO<sub>2</sub> was lower during HFPV at a lower PIP (49). In a sheep smoke/burn model (50), HFPV in conjunction with extracorporeal CO<sub>2</sub>

removal showed improved survival compared to HFPV or low-tidal volume ventilation. There were no differences in hemodynamics or bronchial obstruction, although HFPV alone had less bronchial obstruction than those treated with arterio-venous CO<sub>2</sub> removal (50).

The effects of HFPV on nitrogen washout were studied in an ex-vivo model of adult porcine lungs with normal or low compliance using a HFPV-high [PIP 40 cmH<sub>2</sub>O and continuous positive airway pressure (CPAP) 20 cmH<sub>2</sub>O] or HFPV-low (PIP 30 cmH<sub>2</sub>O and CPAP 10 cmH<sub>2</sub>O) strategy (51). Compared to CMV, both HFPV strategies resulted in similar washout rates as CMV, but at a much lower VT and mean airway pressure (51).

In a rabbit model of gastric aspiration, HFPV improved respiratory mechanics, oxygenation, and markers of lung injury compared to non-protective CMV, and performed similarly to protective CMV and HFOV (52). During HFPV, rabbits required higher doses of anesthetics to reach a predetermined surgical plane of anesthesia with no differences in gas exchange (53). While not confirmed in humans, this could suggest that patients receiving HFPV may require more sedation than those receiving CMV.

### *Bench studies*

Bench models have evaluated VT delivery, the ability to measure accurate VT in clinical practice, humidification, nitrogen washout, and nitric oxide delivery during HFPV. Delivered VT and nitrogen washout during HFPV were affected by changes in elastance and resistance (54). When resistance was increased, the rise in VT was slower; when

**Table 1** Studies on high-frequency percussive ventilation in neonatal and pediatric patients

| Author, year published | Type of study | N  | Pathology, if known   | Findings of HFPV initiation   |
|------------------------|---------------|----|---|---|
| Rizkalla, 2014         | Retrospective | 31 | Acute respiratory failure largely secondary to infectious etiologies                          | Improved gas exchange at lower PIP (median 38 vs. 26 cmH <sub>2</sub> O); improved OI and P/F as early as 12 hours later; decreased PaCO <sub>2</sub> within 6 hours of initiation; initiation did not lead to increased hemodynamic instability or more air leaks  |
| Tawfik, 2016           | Retrospective | 27 | Acute respiratory failure, multiple etiologies  | Most commonly documented reasons for HFPV: secretion management (52%) and ventilation (30%); improved oxygenation, decreased PaCO <sub>2</sub> levels 6 hours after initiation (PIP <30 cmH <sub>2</sub> O, mPaw 16±2.9); complications: hypotension requiring return to CMV (4%), pneumothorax (4%), and bronchoscopy for secretion removal (15%)                                  |
| Paviotti, 2014         | Case series   | 6  | Persistent pulmonary hypertension of the newborn (PPHN); severe hypoxemic respiratory failure | Marked oxygenation improvement with a decrease in OI—achieved without an increase in mPaw and PIP; no change in PaCO <sub>2</sub> values, although hypercarbia is rarely a complicating factor in PPHN; concluded HFPV could play a role in neonatal hypoxemic respiratory failure unresponsive to CMV/HFOV and medical management, especially in centers where ECMO is unavailable |
| Mabe, 2007             | Case report   | 1  | Aspiration pneumonitis from hydrocarbon inhalation  | Mobilization of large amounts of secretions<br>Improvement in oxygenation   |
| Fitzgerald, 2011       | Case report   | 1  | ARDS secondary to post intubation tracheal injury with severe air leak syndrome on VV ECMO    | Prior to ECMO decannulation, marked improvement in secretion clearance; complete expansion of bilateral lungs without disrupting healing trachea  |
| Claudet, 2012          | Case report   | 1  | ARDS secondary to hydrogen sulfide gas intoxication from submersion in a manure tank          | Recovery from respiratory failure   |
| Blondonnet, 2015       | Case report   | 1  | ARDS secondary aspiration pneumonia   | Large improvement in oxygenation and ability to decannulate from ECMO within 24 hours of HFPV initiation with a mPaw of 25 cmH <sub>2</sub> O and PEEP of 15 cmH <sub>2</sub> O   |

HFPV, high-frequency percussive ventilation; PIP, peak inspiratory pressure; CMV, conventional mechanical ventilation; mPaw, mean airway pressure; HFOV, high-frequency oscillatory ventilation.

elastance was increased, the VT reached a plateau quickly, resulting in a longer “plateau” during inspiration. The measured VT total (or total gas delivered during each inspiratory phase) ranged from 710 to 1,820 mL, which is outside the lung protective range, although 300 to 848 mL was exhaled during the inspiratory phase due to passive exhalation following percussive breaths. Changes in elastance and resistance also resulted in changes in the delivered mPaw and PIP with both increasing when elastance and resistance increased. The VT delivered during the percussive breaths was more effected by changes in resistance than in elastance (54).

During HFPV, endotracheal tube cuff deflation resulted in a decrease in proximal airway pressure (Pvent), measured mPaw, and FiO<sub>2</sub> at the simulated carina (55). The lower

FiO<sub>2</sub> was likely due to increased entrainment of ambient air. Pvent was equal to the mPaw at the carina when the cuff was inflated (55). Increasing the percussive rate resulted in decreased VT but no change in the delta pressure with the cuff deflated (56). A study of airway humidification during HFPV found none of the humidification systems tested provided optimal humidity (57).

Gas distribution in a two-compartment lung model with varying elastance and resistance levels demonstrated VT delivery was affected by changes in lung mechanics (58). Nitrogen washout was more efficient at a lower mPaw during HFPV. Despite similar settings at the airway, HFPV was found to deliver 55% of the mPaw compared to PCV (58). Delivered VT can be measured accurately in real time during HFPV with external or portable monitors (59,60).

Elastance and resistance can also be estimated through an external monitor during HFPV with acceptable accuracy (61). It is not possible to precisely deliver inhaled nitric oxide during HFPV (62).

### Conclusion and recommendations for clinical practice

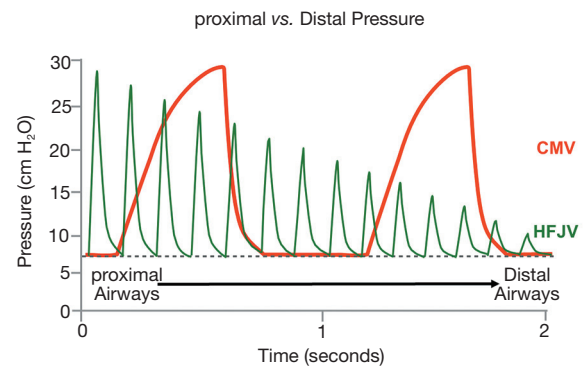
HFPV has a role in the treatment of patients with smoke inhalation or burns. Its use in children and neonates has been shown to improve gas exchange without the need for higher airway pressure. HFPV is purported to improve secretion clearance, yet this has not been objectively demonstrated in children. Bench studies have shown that VT delivery is outside of the currently acceptable lung-protective range; although studies have shown conflicting results, likely due to how individual studies defined VT. Animal and bench models reveal complex cardiopulmonary interactions and further research is needed to elucidate what patient populations may benefit from HFPV. Future studies should attempt to include transpulmonary pressure monitoring, VT, and electric impedance tomography to evaluate the effect of HFPV on lung volumes.

### HFJV

HFJV achieves ventilation through delivery of high-velocity gas using a solenoid activated pinch valve. This results in a pulsating stream of gas at a rate between 240 and 660 cycles per minute and an inspiratory time of 0.02 to 0.034 s (Figure 3). The resulting PIP is attenuated down the respiratory system and theoretically provides lung protective ventilation (63,64). HFJV most often is utilized in premature infants or within neonatal intensive care units (NICUs) (65,66). HFJV requires the use of both a jet ventilator and a conventional ventilator, the later used to provide PEEP and periodic recruitment or “sigh” breaths. The CMV rate is usually set between 0 and 5 breaths per minute and the PIP is set below the HFJV PIP to avoid interruption of jet ventilation during CMV breaths. The use of HFJV in the PICU has been limited to small, single center case series and one outdated RCT (67-69).

### Recent clinical studies of HFJV in the PICU

The use of HFJV in 35 infants (median 2.9 months and 5.2 kg) with acute respiratory failure from multiple etiologies in a quaternary PICU was recently reported (67). HFJV improved CO<sub>2</sub> clearance but had no effect on oxygenation.



**Figure 3** Graphic representation of proximal versus distal pressure during high-frequency jet ventilation (HFJV) compared to conventional mechanical ventilation (CMV). As the HFJV pulses move down the airway, there the pressure amplitude is attenuated, unlike CMV (courtesy of Evan Richards, RR).

HFJV failure was common, with 29% of subjects failing within 4–6 h post initiation and 51% making a successful transition from HFJV back to CMV. Initial HFJV PIP was 46 cmH<sub>2</sub>O with a rate of 360 breaths per minute and mPaw of 14 cmH<sub>2</sub>O. ECMO was required for 26% of subjects and the overall survival was 74% (67).

HFJV was evaluated in a case series of 12 infants (1.7 to 14.2 kg) with respiratory syncytial virus (RSV) failing CMV (68). HFJV was initiated primarily due to hypercapnia although 11/12 patients also met PARDS criteria. The overall survival rate was 91%. The mean partial pressure of CO<sub>2</sub> (PaCO<sub>2</sub>) prior to HFJV decreased by nine mmHg after 24 hours; there was no significant change in oxygenation index (68). Importantly, the HFJV settings used, initiation criteria or detailed data prior to HFJV initiation were not reported.

The use of HFJV in 25 infants with congenital diaphragmatic hernia resulted in significant improvement in pH with a decrease in PaCO<sub>2</sub> (70). The study reported general ventilation guidelines in which the mPaw was <12 cmH<sub>2</sub>O, PIP ≤25 cmH<sub>2</sub>O, mild-moderate permissive hypercapnia (pH >7.25) and target SpO<sub>2</sub> ≥85% but not did not report the specific settings used. Mortality rate was 64% (70). Importantly, congenital diaphragmatic hernia may be managed in both NICUs and PICUs, depending on the center (71). HFJV with heliox as the driving gas was used in an infant with significant barotrauma and hypercapnia despite HFJV. The addition of heliox resulted in improved PaCO<sub>2</sub> levels (72).

### *Clinical studies published before 2000*

#### **Acute hypoxemic respiratory failure**

Smith *et al.* (69) evaluated HFJV in 29 patients with PARDS (mean 1.0 years) and air leak syndrome. Prior to HFJV, PIP was 48 cmH<sub>2</sub>O during CMV and PaCO<sub>2</sub> was 45 mmHg. The survival rate was 69% (69). This study predates the wide-spread adoption of lung-protective ventilation and suggest HFJV may have a role in managing air-leak syndrome.

#### **Post cardiac surgery**

Several studies have evaluated the effect of HFJV on gas exchange and hemodynamics in infants and children with congenital heart disease. These have been small, single center studies with limited applicability in current PICUs.

HFJV was used in nine patients (mean age 9 months) after congenital heart surgery who met pulmonary criteria for ECMO, predominantly due to pulmonary hypertension (73). Ventilation and oxygenation improved during HFJV with similar PIP and mPaw as during CMV with stable hemodynamics. ECMO was avoided in all but one patient. The mortality rate was 33% and one patient developed a pneumothorax (73). HFJV was used in 13 patients (mean age 3.9 years, mean weight 13.9 kg) after the Fontan operation (74). There were no differences in PaCO<sub>2</sub> before, during or after HFJV but adequate support was achieved at a lower mPaw (9.2 *vs.* 4.6 cmH<sub>2</sub>O) with overall improved hemodynamics and cardiac index (74). Current management after the Fontan procedure is early extubation and avoidance of high intrathoracic pressures; it is unclear if HFJV still has a role in the management of children post Fontan as current devices may not be able to effectively ventilate larger children.

When HFJV was used in six infants weighing 2.4 to 5.7 kg post cardiac surgery, ventilation was achieved with lower PIP, significantly lower tracheal pressure (24 *vs.* 14 cmH<sub>2</sub>O) compared to CMV, with no change in measured hemodynamic parameters (75). A similar study evaluated the effect of HFJV on hemodynamics of six infants post cardiac surgery and demonstrated a significant decrease in PIP from 25 to 11 cmH<sub>2</sub>O and reduction in mPaw from 7 to 5 cmH<sub>2</sub>O, although this was likely related to a decrease in set PEEP. There was no relationship between HFJV and cardiac index, although in patients with low cardiac index, HFJV resulted in a 33% increase. There were no other differences in hemodynamic measurements (76).

### *Animal studies of HFJV*

HFJV has been studied in various animal models. Airway pressures and gas exchange were compared between CMV, HFJV, and HFOV in 12 pigs weighing between 10 and 16 kg (77). HFJV resulted in lower PaCO<sub>2</sub>, higher pH, and higher cardiac index with a lower mPaw compared to both CMV and HFOV. Importantly, this study found that the mPaw measured at the proximal airway and the trachea were nearly identical in contrast to a prior study in which tracheal pressure was significantly lower (75). This study examined HFJV in a configuration that may not be used in clinical practice in PICUs and the CMV strategy was not protective. A study of rabbits concluded that HFOV and HFJV cannot be compared on the basis of mPaw and demonstrated that mPaw accurately estimated mean alveolar pressure during HFJV (78). A study comparing HFJV and HFOV in cats with a mean weight of 4.5 kg showed that HFJV resulted in lower PaCO<sub>2</sub> and higher pH at similar airway pressures but no change in oxygenation (79). Transition from HFJV to HFOV in this study resulted in acidosis, increased pulmonary artery pressure, increased PVR, and a decreased cardiac output (79).

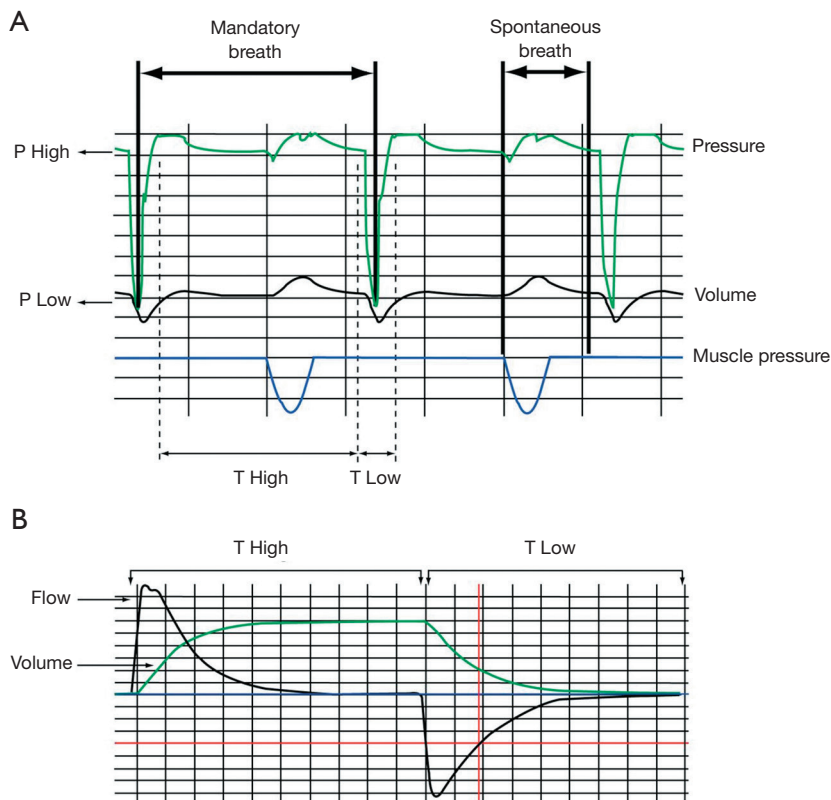
### *Bench studies*

Aerosol delivery during HFJV using magnetic resonance imaging of a phantom lung was lower in comparison to that during HFOV, and both were lower compared to CMV (80). Importantly, this study utilized the MiniHeart nebulizer driven by 2 L/min of flow within the inspiratory limb of the conventional ventilator circuit. A mathematical equation to predict what PEEP needs to be set to match the mPaw when transitioning between HFJV and HFOV suggested that mPaw should be increased by 4 to 6 cmH<sub>2</sub>O when initiating HFJV (81).

### *Conclusion and recommendations for clinical practice*

Data evaluating HFJV in the PICU are limited to small, single center case series, outdated RCTs or physiologic studies without control groups. HFJV may have a role in refractory hypercapnia in children with viral bronchiolitis, in air leak syndrome, and post cardiac surgery to improve hemodynamics, although the impact on more relevant outcomes requires further investigation.





**Figure 4** Pressure (green) and volume (black) over time curve in airway pressure release ventilation (APRV). Shown in the figure: 2 full mandatory breaths (not triggered by muscle effort), and 2 full spontaneous breaths (triggered by muscle effort, in blue) on the top of the mandatory ones. Muscle pressure (blue): the long arrow represents the T high, and the short arrow represents the T low of the mandatory breath. B: Flow (black) and volume (green) over time curve in APRV. T high is the start of the inspiratory flow to the start of expiratory flow, T low is the start of expiratory flow to the beginning of the next inspiratory flow. The 2 red intersecting lines are at 50% of the peak expiratory flow. [Reproduced with permission from: Daoud EG, Farag HL, Chatburn RL. Airway pressure release ventilation: what do we know? *Respir Care*. 2012;57(2):282-92.]

## APRV

APRV is a time-cycled, pressure controlled, synchronized intermittent mandatory ventilation mode generally utilized with an inverse I:E ratio. It was first described in 1987 by Stock and Downs as a strategy to maintain lung volume, maximize alveolar recruitment, and avoid overdistension and collapse (82-86) (*Figure 4*). APRV maintains PIP (or P-high) with brief cyclical releases to enhance CO<sub>2</sub> removal, with unrestricted spontaneous breathing during P-high. APRV has been used primarily as a rescue strategy in patients with ARDS or refractory hypoxemia (84,87,88). Detailed descriptions of the intricacies of APRV are beyond the scope of this paper, but have been reviewed elsewhere (84,86,89). A recent meta-analysis of adult studies

found that APRV was associated with a higher number of ventilator free days, lower ICU length of stay, lower hospital mortality, and no significant adverse effects (90). These results need to be interpreted cautiously due to the low quality of the included trials and the fact that many control groups did not receive lung-protective ventilation. Importantly, what defines APRV and how it is used in clinical practice in adults varies widely (91,92).

Proposed advantages of APRV include lung recruitment, improved oxygenation, unrestricted spontaneous breathing, improved hemodynamics, better V/Q matching, and reduction in sedative requirements. Disadvantages of APRV include difficulty of controlling VT, concern for atelectrauma during releases (especially in lung units with low compliance and resistance), and exposure to high

transpulmonary pressure during spontaneous breathing at P-high. Current data evaluating APRV in children are limited to single center case series as a rescue mode for patients with refractory hypoxemia and one small, single center RCT (93-103).

### *Prospective clinical studies in children*

A single center RCT comparing low VT CMV to APRV in PARDS was terminated early after enrolling 52 subjects due to a higher mortality rate (54% *vs.* 27%) in the APRV group (98). There were significant differences in baseline characteristics between the groups, with the APRV group having lower baseline P/F ratio and higher oxygenation index, although VT, P/F ratio and oxygenation index were similar 12 h post randomization and mPaw was approximately 2 cmH<sub>2</sub>O higher in the APRV group throughout the study. After controlling for illness severity, APRV was associated with a risk ratio of 2.02 for mortality (98).

A prospective, crossover study comparing APRV to CMV in children after Tetralogy of Fallot, Glenn or Hemi-Fontan, or Fontan procedures found that APRV improved pulmonary blood flow, although SvO<sub>2</sub> and other indexes of oxygenation were similar on both modes (100). APRV did not adversely affect hemodynamics using a P-high of 13–20 cmH<sub>2</sub>O (100). An increase in pulmonary blood flow was observed only when patients in APRV were spontaneously breathing. There were no differences between groups in global hemodynamics measurements or gas exchange. This study revealed that during releases, the pleural pressure was negative despite a reasonably set T-low of 0.3–0.5 seconds. In contrast, the end-expiratory transpulmonary pressure in the CMV group was at or above 0 cmH<sub>2</sub>O throughout (100).

### *Retrospective case series*

A retrospective analysis of 104 pediatric patients with ARDS, who were transitioned to either APRV or HFOV for refractory hypoxemia on CMV found that improvement in oxygenation after transition was associated with improved survival, independent of the rescue mode used (101). A similar study found that survival in immunocompromised patients with ARDS was significantly associated with improved oxygenation 24 h after transition to APRV or HFOV (102). A recent retrospective analysis of 30 pediatric patients with severe PARDS transitioned from CMV to APRV for refractory hypoxemia found that the SpO<sub>2</sub>/

FiO<sub>2</sub> ratio increased from 132 to 165, likely secondary to increased mPaw with a lower PIP, and a mortality rate of 17% (103). Previous small pediatric case series/case reports also observed improved oxygenation at lower peak airway pressure (93,94,97,99) and no adverse hemodynamic effects (95,96). A retrospective study comparing outcomes of rescue APRV (n=22) or HFOV (n=25) found no differences between the two groups (104). An important consideration during APRV is that the reduction in PIP may not result in a reduction of end-inspiratory transpulmonary pressure, as the patient's breathing effort will add to the P-high. Thus, a reduction of PIP during APRV may result in excessive transpulmonary pressure even when the P-high is within the lung-protective range, especially if tube compensation or pressure support are used.

### *Animal models*

Multiple investigators have sought to examine the effects of APRV on lung microstrain and alveolar recruitment in animal models. In a porcine model of combined brain injury/ARDS, there were no differences in gas exchange or histopathology between APRV and an ARDSnet-based CMV strategy, although microdialysis trends suggested increased brain ischemia in the APRV group (105). APRV utilizing varying ratios of peak expiratory flow rate (PEFR) was compared to CMV with multiple levels of PEEP in a rat model of lung injury. During APRV, peak expiratory flow rate (PEFR) is terminated at a percentage of the peak expiratory flow, prior to complete exhalation, in order to create intrinsic PEEP as an alternative to extrinsically set PEEP. When this strategy is used, P-low is generally set to 0 cmH<sub>2</sub>O (86,91). They found that both a PEEP greater than 16 and APRV with a PEFR targeted at 75% minimized microstrain, however APRV also improved alveolar recruitment (106). A similar study found a PEFR target of 75% during T-low resulted in the least alveolar microstrain (107). In other animal models, APRV has had a favorable effect on dynamic alveolar homogeneity (108) and has also led to improved mucous clearance (109). APRV was found to reduce inflammation and pulmonary edema in a rabbit model of ARDS (110).

Spontaneous breathing during APRV has been associated with improved gastrointestinal (111,112), renal (113), and nervous system perfusion (114), and may reduce risk of lung injury (115). In a rat model, preemptive application of APRV to a normal lung prevented development of ARDS-like histopathology (116). In a porcine model of indirect

lung injury, animals treated with APRV did not develop ARDS (117). It is important to note that the control groups in these studies did not receive lung-protective ventilation. APRV was compared to the ARDSnet protocol to examine whether ARDS could be prevented (118). The APRV group had preserved oxygenation with lung histology showing preserved lung architecture and less pulmonary edema. APRV was also shown to prevent ARDS in a rat model of hemorrhagic shock (119). Importantly, the vast majority of these animal studies originate from a single research group and most have used an ischemic-reperfusion sepsis model to induce extrapulmonary ARDS. The applicability of these results to primary pulmonary ARDS is limited. Lastly, these pre-clinical studies have yet to be translated to clinical practice.

### ***Bench models***

A case report demonstrated that VT during APRV ranged from 4 to 12 mL/kg and the patient had CT scan consistent with ventilator induced lung injury. In a bench model, control of VT and auto-PEEP could not be achieved even in a passive model (120). In a study of APRV using a high-fidelity simulator, auto-PEEP was found to be highly variable and resulted in unstable lung volumes (121). In a lung model, VT delivery during APRV was lower when compared to other modes (122). Spontaneous breathing during APRV results in variable VT and carries a risk of high VT delivery (123), yet aerosol deposition is increased compared to other modes (124). When compared to BiPAP with similar settings, APRV resulted in higher mPaw and higher total PEEP, and PEEP could not be predicted by lung mechanics (125). There is considerable variability in auto-PEEP during APRV among six commercially available ventilators (126).

### ***Conclusion and recommendations for clinical practice***

There is controversy on the choice of optimal settings, indication, and clinical efficacy of APRV. Current data have shown short-term improvements in oxygenation; however, this may not translate into improved patient outcomes and a pediatric RCT has suggested possible harm associated with APRV (98). Bench and animal studies have shown it to be a complex mode where VT and auto-PEEP cannot be easily controlled, even under ideal conditions. Importantly, its performance also varies across different ventilator platforms. High-quality, multi-center RCTs studies are

needed to elucidate the role of APRV in PARDS. Other areas of interest requiring further study are the utility of APRV during ECMO and as a strategy to prevent the development of lung injury.

### **NAVA**

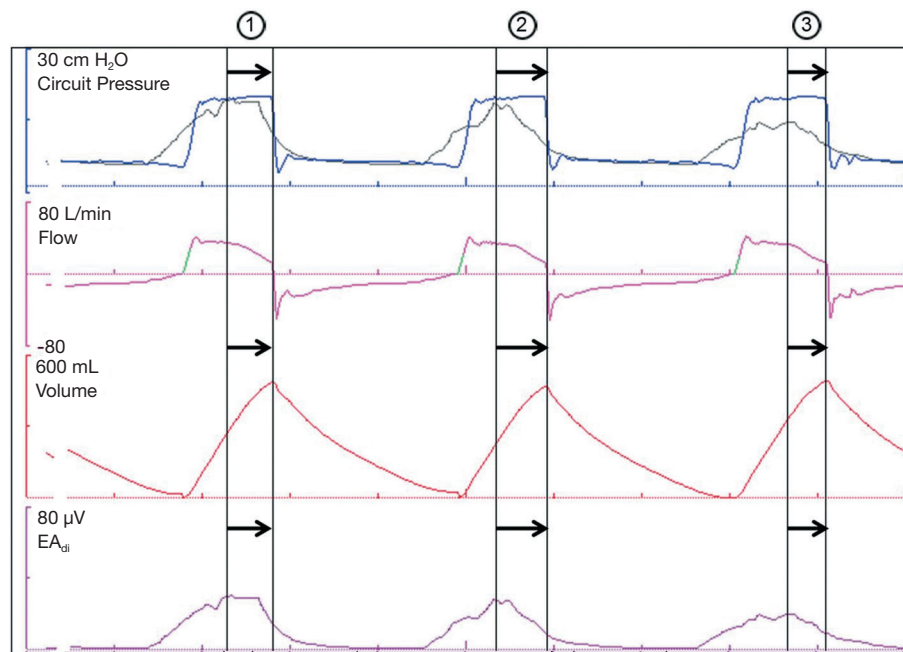
NAVA is an advanced mode of mechanical ventilation in which breaths are synchronized to the electrical activity of the diaphragm (EAdi) using a proprietary ventilator and specialized gastric tube containing an array of electrodes positioned in the esophagus at the level of the diaphragm (127). The NAVA level is adjusted to provide positive pressure in proportion to the patient's effort, or EAdi, and synchronizes to the patient's neural respiratory drive (127). The EAdi signal is processed to provide the highest possible quality and is not artificially influenced by changes in lung volume, muscle length, chest wall configuration, intraabdominal pressure, and applied end-expiratory pressure (128-130) (*Figure 5*). NAVA is can be used in both invasive and non-invasive ventilation.

### ***Adult data***

A meta-analysis found NAVA improved ventilator synchrony but had no effect on patient outcomes such as length of stay, ventilator free days, or mortality (131). A recent RCT of critically ill adults expected to be mechanically ventilated for more than 72 hours found that NAVA resulted in four more ventilator free days, and 4.1 fewer days on mechanical ventilation, although there was no effect on mortality (132). A smaller RCT in patients at high risk of prolonged ventilation found NAVA to be associated with more ventilator free days and a decrease in mortality (133).

### ***Clinical use of NAVA in the PICU***

A recent meta-analysis 464 patients treated with NAVA or CMV showed NAVA to be associated with improved ventilator synchrony, lower PIP, and higher oxygen saturation (131). Crossover studies of NAVA in the PICU have consistently demonstrated improved patient-ventilator synchrony (134-139). An asynchrony rate between 12% and 73% has been described during CMV compared to zero to 20% during NAVA (140). NAVA has been shown to improve COMFORT scores (138,141) and reduce sedation needs (142). An RCT of 170 subjects observed shorter ICU LOS using NAVA, although there was no difference in



**Figure 5** Pressure, flow, volume, and electrical activity of the diaphragm (EAdi) waveforms from a patient on pressure support ventilation, and the presumed pressure curve (grey) if the patient was on neurally adjusted ventilatory assist (NAVA), with a preset NAVA level not shown. Breath 3 demonstrates expiratory timing asynchrony: there is continued mechanical inflation after the start of the neural expiration, causing a delay between the neural expiration and the mechanical deflation. [Reproduced with permission from Verbrugge W, Jorens PG. Neurally adjusted ventilatory assist: a ventilation tool or a ventilation toy? *Respir Care*. 2011;56(3):327-35.]

time on mechanical ventilation (142). In infants recovering from PARDS, NAVA showed improved synchrony, lower PIP, and a tendency toward higher VT (141). NAVA-triggered breaths have been shown to have less trigger delay and shorter system response time in infants with bronchiolitis (143). In another report of three children with bronchiolitis, NAVA was found to reduce PIP, improve patient-ventilator synchrony, and reduce  $\text{FiO}_2$  requirement (144). In a selected population of difficult to wean pediatric patients recovering from moderate PARDS, NAVA improved synchrony and resulted in better oxygenation compared to PSV (145).

### Congenital heart disease

In children with congenital heart disease, NAVA has been shown to improve ventilator synchrony (134) with lower PIP and  $\text{mPaw}$  (146-148). NAVA had no effect on hemodynamics in the majority of patients post cardiac surgery (149). More recently, in a physiological cross-over study, NAVA was compared to PSV and PSV SIGH (PSV with 1 machine breath per minute) in hypoxemic infants after cardiac surgery. NAVA resulted in better patient-ventilator synchrony compared with

pressure support but there was no difference in oxygenation and static compliance of the respiratory system (150).

In a small retrospective series, NAVA was used in six pediatric patients with severe respiratory failure on VV ECMO. NAVA was initiated when diaphragmatic electrical activity (EAdi) allowed for triggering. Proportionate to EAdi (1.8–26  $\mu\text{V}$ ), initial PIP ranged from 21 to 34  $\text{cmH}_2\text{O}$ , and VT from 3 to 7  $\text{mL/kg}$ . During weaning, PIP increased proportionally to EAdi increase (5.2–41  $\mu\text{V}$ ), with VT ranging from 6.6 to 8.6  $\text{mL/kg}$ . Improved synchrony during NAVA may help patients liberate from ECMO or help assess readiness for sweep gas trials (151).

### Animal models

In a rabbit model, the use of NAVA was associated with less ventilator-induced lung injury, attenuated systemic inflammation, and preserved cardiac and kidney function (152). Other animal models have also demonstrated more efficient and synchronous ventilation (153,154) with unloading of respiratory muscles without excessive VT and low  $\text{mPaw}$  (153). In animals recovering from lung

injury, NAVA reduced asynchrony, trigger delay, and the pressure time product (155). In animals ventilated without PEEP after ALI, EAdi level was increased during the exhalation phase (128,156). Application of PEEP in a step-wise fashion showed a dose-response reduction in tonic activity and re-institution of phasic breathing (156). In an anesthetized and spontaneously breathing rabbit model, adjusting pressure continuously in proportion to both inspiratory and expiratory EAdi showed a reduction in inspiratory effort compared to triggered NAVA (157). Recent experimental study demonstrates the use of EAdi to control negative pressure ventilation in small animals (158).

In an animal model of mild ARDS, NAVA showed that increasing PEEP reduced respiratory rate, atelectasis, recruitment/derecruitment, and breath size variability but increased VT and transpulmonary pressure (159). NAVA may be superior to PSV in preventing diaphragm injury during mechanical ventilation, and both NAVA and PSV were associated with less atrophy than CMV (160).

### ***Conclusion and recommendations for clinical practice***

NAVA can be safely applied in pediatric patients and is associated with improvements in ventilator synchrony and sedation requirements. These benefits are based on a small number of studies and have not translated into improved survival, ventilator-free days or time on mechanical ventilation. A large multicenter RCT to comparing NAVA and CMV in children is needed. Current evidence would suggest NAVA be applied in difficult to liberate patients or those in whom asynchrony has been observed or is highly suspected.

### **Summary of advanced ventilator modes in the PICU and future directions for research**

The evidence supporting advanced ventilator modes is weak and consists largely of single center case series although some RCTs have been performed. This may have resulted in publication bias as centers with less favorable experiences with HFPV, HFJV, and APRV in particular, may not have published their results. Animal and bench models illustrate the complexities of different modes and the challenges of applying these clinically. Importantly, animal and bench models have often produced contradictory results, which underscores the need for additional research. Some modes are proprietary to certain ventilators, are expensive, or may only be available at well-resourced centers.

Future efforts should include large, multi-center

observational, interventional, or adaptive design trials of different rescue modes (e.g., PROSpect trial), evaluate their use during ECMO, and should incorporate assessments through volumetric capnography, electric impedance tomography, and transpulmonary pressure measurements, along with precise reporting of ventilator parameters and physiologic variables.

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