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High frequency percussive ventilation in pediatric acute respiratory failure

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Abstract

Objective: High frequency percussive ventilation (HFPV) is used in acute respiratory failure, but is poorly described in pediatrics. We aimed to describe the clinical characteristics, ventilator settings, and outcomes of a large pediatric cohort, and to determine predictors of who would benefit from HFPV.

Hypothesis: Gas exchange 2 h after HFPV initiation predicts success.

Design: Single center retrospective cohort study testing association between gas exchange 2 h after HFPV initiation with success, defined a priori.

Patients: Intubated children on HFPV for ≥2 h from 2012 to 2018.

Methods: We described indications, ventilator settings, and gas exchange immediately before, 2 h after, and at termination of HFPV. Univariate and multivariate regression tested association of oxygenation and ventilation after HFPV initiation with success. Areas under the receiver operating characteristic (AUROC) curve and adjusted odds ratios (aORs) were computed.

Results: We performed 237 courses of HFPV in 193 children (22% non-survivors), of which 162 (68%) were successful. In univariate analysis, pH (AUROC, 0.65) and PCO_2 (AUROC, 0.66) 2 h after HFPV predicted success. In multivariate analysis, pH (aOR: 1.67 per 1 *SD*; 95% confidence interval [CI]: 1.19–2.35), PCO_2 (aOR: 0.49 per 1 *SD*; 95% CI: 0.31–0.79), and oxygenation index (aOR: 0.66 per 1 *SD*; 95% CI: 0.44–0.97) 2 h after HFPV initiation were associated with success.

Conclusion: We describe the largest cohort of HFPV to date, with detailed description of indications and settings. Gas exchange after 2 h of HFPV was independently associated with success.

KEYWORDS

ARF, HFPV, high frequency percussive ventilation, high frequency ventilation, nonconventional ventilation

1 | INTRODUCTION

Acute respiratory failure (ARF) is the most common indication for admission to pediatric intensive care units (PICU) and contributes to significant morbidity and mortality. Invasive ventilation is required in approximately 30% of PICU admissions. Alternative ventilator modes have been used for refractory hypoxemia or hypercarbia on conventional mechanical ventilation, often with little evidence for appropriate patient selection, ventilator management, or efficacy.

High frequency percussive ventilation (HFPV) uses time cycled, pressure-controlled ventilation with superimposed percussion throughout the respiratory cycle as an alternative to conventional

ventilation.[1–3] The pneumatic compressions that drives the percussion helps promote secretions clearance and ventilation. HFPV was initially utilized for those with burns[4,5] and secretion clearance,[6,7] but was eventually used in refractory acute respiratory distress syndrome (ARDS).[1,3,8,9] In both pediatrics[3] and adults,[8] HFPV has been shown to improve oxygenation without increasing the peak inspiratory pressures (PIP), consistent with the tenets of lung-protective ventilation.

However, while better studied in adult ARF,[10] HFPV remains relatively understudied in pediatric ARF, with the largest case series comprising 31 children.[3] Specifically, it is unknown which patients will benefit from HFPV. Additionally, uncertainty surrounding how best to utilize HFPV has contributed to reluctance of widespread adoption of HFPV for refractory ARF in pediatrics. The Children's Hospital of Philadelphia (CHOP) PICU has used HFPV since 2010, and has amassed the largest pediatric experience to date. Therefore, we retrospectively evaluated children with ARF that used HFPV at our institution to better evaluate the clinical characteristics, HFPV settings, and adjunct medical therapies used with HFPV. Our purpose was two-fold: (1) to describe the clinical characteristics, ventilator settings, and outcomes of a large pediatric cohort on HFPV; and (2) to determine early predictors of who will benefit from HFPV. We hypothesized that gas exchange 2 h after HFPV initiation would predict HFPV success in pediatric ARF.

2 | METHODS

2.1 | Study design and patient selection

This was a retrospective cohort study in the CHOP PICU approved by the Institutional Review Board, with requirement for informed consent waived. All patients from January 1, 2012 to June 30, 2018 on invasive HFPV for at least 2 h in the PICU were included. We chose this timeframe to exclude subjects included in our initial report on HFPV.[3] We defined a course of HFPV as lasting at least 2 h and ending when off of HFPV for greater than 2 h. If a patient was on HFPV, converted to a different form of ventilation for greater than 2 h, then went back on HFPV, this was considered a different course of HFPV within the same encounter. There were no exclusion criteria.

2.2 | Exposures and outcomes

Our primary exposures were blood gas analyses (pH and PCO_2) and oxygenation. Our primary outcome was success versus failure for reason of discontinuation of HFPV. A successful course of HFPV was determined by chart review of notes, with documentation of improvement or weaning off HFPV onto another mode of ventilation or extubation as the reason for discontinuation of HFPV. Reasons for HFPV failure were categorized a priori into eight mutually exclusive categories: persistent hypercarbia, persistent hypoxemia, persistent hypercarbia and hypoxemia, persistent secretions, asynchrony, air leak, transport, or death. The determination of success or failure and category of failure were independently verified by two investigators. Disagreements were discussed until a unified determination of success or failure and a single reason for failure were assigned for every HFPV course. Our secondary outcomes were PICU mortality and ventilator-free days (VFDs) at 28 days, both limited to the first course for those patients with more than one course of HFPV.

2.3 | HFPV strategy

CHOP uses the VDR-4 with the TurboHub Phasitron (Percussionaire Corp). We do not use hypertonic saline, N-acetylcysteine, heparin, or dornase on HFPV due to concerns of clogging the Phasitron. Decisions to initiate or terminate HFPV are at the discretion of the attending physician. Adjustments to HFPV settings are made on the basis of invasive (blood gases) and noninvasive (pulse oximetry and transcutaneous CO_2 monitors) measurements of oxygenation and ventilation, with preferential reduction in PIP with improving ventilation and preferential reductions in FIO_2 to ≤0.60 with improving oxygenation. Inspiratory or expiratory ratio was started and preferentially maintained at 1:1. Up until October 2014, pressures were measured using a manometer connected to the inhalational limb of the circuit adjacent to the proximal endotracheal tube attached to the VDR-4 which continuously displayed measured pressures. After October 2014, we transitioned to the Digital Multimeter Manometer. Pressure measurements between the two different manometers were unchanged.

2.4 | Data collection

We abstracted demographics, pediatric risk of mortality (PRISM) III score at 12 h, diagnoses, co-morbidities, and immunocompromised status. We collected reasons for going on HFPV (oxygenation, ventilation, both oxygenation and ventilation, secretions, lung rest while on extracorporeal membrane oxygenation [ECMO]) based on two-person chart review. We recorded ventilator settings before transitioning to HFPV, 2 h after starting HFPV, at termination of HFPV, and 2 h after terminating HFPV. We also recorded all available blood gases (arterial and venous), any adjunct therapies (inhaled nitric oxide [iNO], neuromuscular blockade, and corticosteroids), respiratory treatments (albuterol, hypertonic saline, intermittent percussive ventilation treatments), and hemodynamics (heart rate, mean arterial pressure, vasopressor score) pre-HFPV and 2 h after starting HFPV. We also recorded use of ECMO during HFPV and development of air leak.

We recorded length of invasive ventilation before HPFV, length of HFPV use, and length of total ventilation. Freedom from invasive ventilation for 48 h defined ventilator duration; if a subject was re-intubated after 48 h, the additional ventilator days were counted towards the total. We also recorded the outcome PICU mortality.

TABLE 1 Demographics stratified by HFPV success

Variable	All (*n* = 237)	HFPV Success (*n* = 162)	HFPV failure (*n* = 75)	*p*
Age (years) (*n* = 193)	3 (1.2, 12)	2.8 (1.2, 9)	4 (1.1, 15)	.241
PRISM III at 12 h (*n* = 193)	8 (3, 15)	8 (3, 16)	7 (3, 12)	.628
Immunocompromised (%) (*n* = 193)	35 (18)	20 (16)	15 (23)	.233
Days of ventilation pre-HFPV	5 (2, 15)	4 (2, 13)	7 (2, 20)	.122
Reason for HFPV (%)				.286
Hypercarbia	75 (32)	52 (32)	23 (31)	
Hypoxemia	39 (16)	30 (19)	9 (12)	
Secretions	86 (36)	59 (36)	27 (36)	
ECMO	8 (3)	6 (4)	2 (3)	
Other	29 (12)	15 (9)	14 (19)	
Pre-HFPV mode (%)				.325
Pressure Control	94 (40)	60 (37)	34 (45)	
PRVC	78 (33)	56 (35)	22 (29)	
APRV	8 (3)	5 (3)	3 (4)	
HFOV	39 (16)	27 (17)	12 (16)	
NIPPV	8 (3)	8 (5)	0	
Intubated to HFPV	10 (4)	6 (4)	4 (5)	
Pre-HFPV				
V_T (ml/kg) (*n* = 169)	6.9 (5.3, 8)	7 (5.4, 8.1)	6.8 (5.3, 7.8)	.617
PIP (cmH_2O) (*n* = 172)	33 (28, 39)	32 (26, 38)	34 (28, 41)	.112
PEEP (cmH_2O) (*n* = 172)	10 (8, 12)	10 (8, 12)	12 (9, 13)	.320
mPaw (cmH_2O) (*n* = 219)	19 (16, 23)	18 (15, 22)	20 (16, 27)	.014
Rate (*n* = 172)	28 (20, 35)	26 (18, 35)	30 (22, 35)	.253
pH (*n* = 219)	7.29 (7.21, 7.38)	7.30 (7.22, 7.38)	7.28 (7.19, 7.38)	.269
$PaCO_2$ (*n* = 219)	66 (53, 83)	64 (51, 82)	69 (53, 94)	.094
OI (*n* = 219)	16.6 (8.6, 26.9)	15 (8.4, 25.6)	18.6 (9.7, 31.4)	.132
2 h after HFPV				
PIP (cmH_2O)	34 (28, 40)	34 (28, 38)	40 (30, 44)	.001
PEEP (cmH_2O)	8 (8, 10)	9 (8, 10)	8 (8, 12)	.501
mPaw (cmH_2O)	23 (19, 26)	22 (19, 25)	24 (19, 29)	.029
Convective rate	24 (20, 30)	24 (20, 30)	25 (20, 30)	.227
Percussive rate	600 (500, 600)	600 (550, 600)	550 (500, 600)	.011
pH	7.36 (7.29, 7.44)	7.37 (7.31, 7.45)	7.33 (7.26, 7.39)	<.001
$PaCO_2$	56 (45, 71)	52 (42, 66)	66 (51, 82)	<.001
OI	14.3 (9.2, 23.8)	13.6 (8.8, 20.2)	16.5 (9.3, 29.3)	.060
Duration of HFPV (days)	4 (2, 7)	5 (3, 8)	3 (2, 6)	.002
Air leak on HFPV (%)	18 (8)	5 (3)	13 (17)	<.001
PICU mortality (%) (*n* = 193)	42/193 (22)	11/129 (9)	31/64 (48)	<.001

Abbreviations: APRV, airway pressure release ventilation; ECMO, extracorporeal membrane oxygenation; HFOV, high frequency oscillatory ventilation; HFPV, high frequency percussive ventilation; mPaw, mean airway pressure; NIPPV, noninvasive positive pressure ventilation; OI, oxygenation index; PEEP, positive end-expiratory pressure; PICU, pediatric intensive care unit; PIP, peak inspiratory pressure; PRISM III, pediatric risk of mortality III; PRVC, pressure-regulated volume control; VT, tidal volume.

2.5 | Equations and definitions

The vasopressor-ionotropic score[11] equaled: dopamine dose (mcg/kg/min) + dobutamine dose (mcg/kg/min) + 100 x epinephrine dose (mcg/kg/min) + 10 x milrinone dose (mcg/kg/min) + 10,000 x vasopressin dose (units/kg/min) + 100 x norepinephrine dose (mcg/kg/min). For oxygenation, if an arterial blood gas was available, we used the oxygenation index (OI): $(FiO_2 \times mPaw \times 100)/PaO_2$, where mPaw is the mean airway pressure. For those without an arterial blood gas, the oxygen saturation index (OSI) was used: $(FiO_2 \times mPaw \times 100)/SpO_2$, ensuring $80\% \leq SpO_2 \leq 97\%$.[12] OSI was converted to OI for all analyses using accepted equations.[12] Immunocompromised status required the presence of an immunocompromising diagnosis (oncologic, immunologic, rheumatologic, or transplant) and active or recent immunosuppressive chemotherapy.[13]

2.6 | Statistical analysis

Continuous data are reported as mean or median (interquartile range [IQR]) for normally and nonnormally distributed variables. Variables were compared between HFPV successes and failures using Wilcoxon signed-rank test for paired values. Unadjusted blood gas variables (pH, PCO_2, OI) 2 h after HFPV initiation were tested for ability to discriminate HFPV success using area under the receiver operating characteristic (AUROC) curve, excluding those patients on ECMO during HFPV because of unreliability of blood gas metrics. We chose 2 h so as to minimize the timeframe after HFPV initiation and limit the number of potential co-interventions other than HFPV which could affect oxygenation and ventilation. Blood gas variables 2 h after HFPV initiation were also tested for independent association with HFPV success after adjustment for PRISM III, immunocompromised status, OI before HFPV, and PCO_2 before HFPV using multivariable logistic regression, again excluding patients on ECMO. In a sensitivity analysis, we repeated testing the association between blood gas variables and HFPV success after restricting to subjects with arterial blood gases.

Additionally, we tested patients' blood gas metrics during their first course of HPFV for association with PICU mortality using multivariable logistic regression and for association with VFDs using multivariable competing risk regression with extubation as the primary outcome and death as the competing risk censoring after 28 days, adjusting for the same confounders as before and again excluding subjects on ECMO.

3 | RESULTS

3.1 | Patient characteristics at HFPV initiation

Overall, 237 patient courses of HFPV in 193 children occurred over the study period. Of those courses, 162 (68%) were successful, while 75 (32%) were designated a failure (Table 1). HFPV successes and failures had similar demographics, severity of illness, and pre-HFPV ventilator support. The most common indications for HFPV were secretion management (36%) and hypercarbia (32%). Indications for HFPV did not differ by eventual success or failure. Eight subjects (3%) were on HFPV for lung recruitment during ECMO,[14] as we have previously described. Patients most commonly transitioned to HFPV after conventional ventilation (73%), with a minority (7%) being initiated immediately after intubation, with or without preceding noninvasive ventilation. Mortality was 22% and was higher among HFPV failures.

Ventilator settings before HFPV initiation were with low tidal volumes (median: 6.9 ml/kg) and high PIPs (median 33 cmH_2O). Median OI was consistent with severe ARDS (median OI: 16.6), and PCO_2 was high (median: 66 mmHg). Other than mPaw, ventilator pressures and gas exchange metrics before HFPV initiation did not differ between eventual HFPV successes or failures (Table 1).

3.2 | After HFPV initiation

After 2 h of HFPV, PIP ($p = .001$), mPaw ($p = .029$), and ventilation (pH and PCO_2, both $p < .001$) were all worse in the group with eventual HFPV failure (Table 1 and Figure 1). Improvements in pH and PCO_2 were driven by improvements in subjects started on HFPV for secretions and hypercarbia (E-Figure 1). There was no change in use of albuterol, neuromuscular blockade, corticosteroids, or iNO 2 h after HFPV initiation (E-Table 1). There was no change in hemodynamics (blood pressure or heart rate) or in vasopressor support 2 h after HFPV initiation.

The starting PIP on HFPV was similar to the PIP on conventional immediately before initiation ($p = .265$). However, mPaw on HFPV was higher (median 19 cmH_2O pre-HFPV vs. median 23 cmH_2O at 2 h; $p < .001$; Table 1) due to the longer inspiratory ratio (1:1 at 2 h in 236 of 237 courses) in HFPV. The convective rate was decreased after starting HFPV (median 28 pre-HFPV vs. median 24 at 2 h; $p < .001$). Percussive rate on HFPV was started at median 600 (IQR: 500, 600).

3.3 | At HFPV termination

Median duration of HFPV was 4 days, with those that were successful on longer (median 5 days) versus those that failed (median 3 days; $p = .002$; Table 1). HFPV was successful in 162 (68%) of courses (E-Table 2). The most common reasons for HFPV failure were persistent hypoxemia or hypercarbia. Seventeen subjects died while receiving HFPV. At discontinuation, HFPV failures had higher pressures than did those with successful courses (E-Table 3). Successful HFPV courses transitioned at median HFPV PIP of 28 cmH_2O and median mPaw of 19 cmH_2O. HFPV successes transitioned to conventional ventilation or were extubated in 97% of cases, compared with 67% of those with HFPV failure ($p < .001$). Subjects with HFPV failure transitioned to high frequency oscillatory ventilation

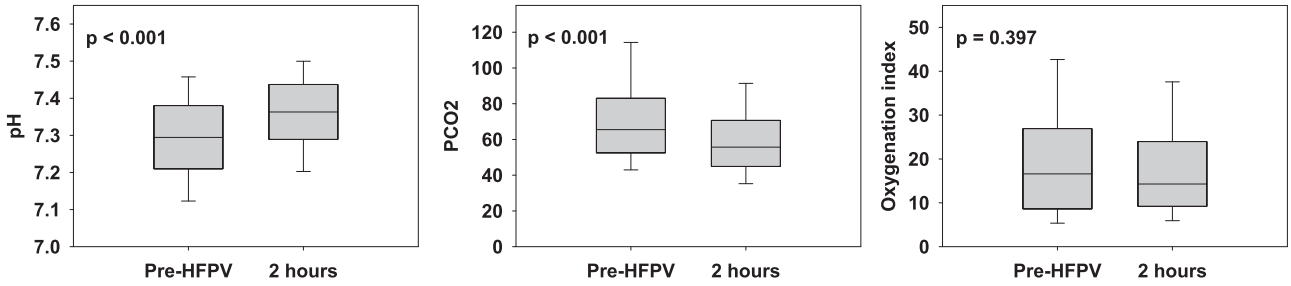

FIGURE 1 Comparisons of pH, PCO_2, and oxygenation index pre-HFPV and 2 h post-HFPV. *p* Values are the results of signed rank test for paired values. HFPV, high frequency percussive ventilation

(HFOV) at a higher rate (31%) compared to those with successful HFPV courses (1%).

3.4 | Predicting HFPV success

Both pH and PCO_2 improved by 2 h of HFPV irrespective of eventual HFPV success or failure, albeit with larger improvements in eventual successful courses (Figure 2). Both pH (AUROC: 0.65; 95% CI: 0.57–0.73) and PCO_2 (AUROC 0.66, 95% CI 0.58–0.74) modestly discriminated HFPV success (E-Table 4). After adjusting for confounders, pH (adjusted odds ratio [aOR] 1.67 per increase in 1 *SD*, 95% CI: 1.19–2.35), PCO_2 (aOR: 0.49 per 1 *SD* increase; 95% CI: 0.31–0.79), and OI (aOR: 0.66 per 1 *SD* increase; 95% CI: 0.44–0.97) 2 h after HFPV initiation were independently associated with HFPV success (Table 2). Results were similar when restricted to subjects with arterial blood gases (E-Table 5).

3.5 | Predicting mortality and VFDs at 28 days

When looking at a subjects' first course of HFPV, neither pH, PCO_2, nor OI at 2 h of HFPV were associated with PICU mortality (Table 3).

TABLE 2 Independent association of variables with HFPV success[a]

Variable	Odds ratio[b,c] (95% confidence interval)	*p* Value
pH 2 h after HFPV	1.67 (1.19–2.35)	.003
PCO_2 2 h after HFPV	0.49 (0.31–0.79)	.003
OI 2 h after HFPV	0.66 (0.44–0.97)	.036

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFPV, high frequency percussive ventilation; OI, oxygenation index; PRISM III, pediatric risk of mortality III.

[a]Excluding patients on ECMO during HFPV.

[b]Adjusted for PRISM III, immunocompromised status, and PCO_2 and OI pre-HFPV.

[c]Variables are standardized (mean = 0, *SD* = 1).

Higher PCO_2 2 h after HFPV initiation was associated with lower probability of extubation by 28 days (adjusted subdistribution hazard ratio 0.45 per 1 *SD* increase; 95% CI: 0.31–0.66), equivalent to fewer VFDs.

4 | DISCUSSION

We describe the largest cohort of adult or pediatric HFPV to date, with detailed review of ventilator settings, ancillary therapy use, and adverse events pre- and post-HFPV. Gas exchange after 2 h of HFPV were independently associated with success, and metrics of ventilation (pH and PCO_2) consistently predicted eventual HFPV success in pediatric ARF. Patients with successful courses had improved

TABLE 3 Independent association of variables with outcomes[a]

Variable[a]	Odds ratio[b,c] (95% confidence interval)	*p* Value
PICU mortality		
pH 2 h after HFPV	0.71 (0.48–1.06)	.094
PCO_2 2 h after HFPV	1.52 (0.89–2.62)	.128
OI 2 h after HFPV	1.08 (0.65–1.81)	.770
	Subdistribution hazard ratio[b,c,d] (95% confidence interval)	
Probability of extubation		
pH 2 h after HFPV	1.22 (0.96–1.55)	.098
PCO_2 2 h after HFPV	0.45 (0.31–0.66)	<.001
OI 2 h after HFPV	1.02 (0.72–1.45)	.912

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFPV, high frequency percussive ventilation; PICU, pediatric intensive care unit; OI, oxygenation index; PRISM III, pediatric risk of mortality III.

[a]Limited to first HFPV exposure if multiple exposures; excluding patients on ECMO during HFPV.

[b]Adjusted for PRISM III, immunocompromised status, and $PaCO_2$ and OI pre-HFPV.

[c]Variables are standardized (mean = 0, *SD* = 1).

[d]SHR < 1 implies increase in variable (e.g., PCO_2) associated with lower probability of extubation by Day 28 (i.e., fewer VFDs).

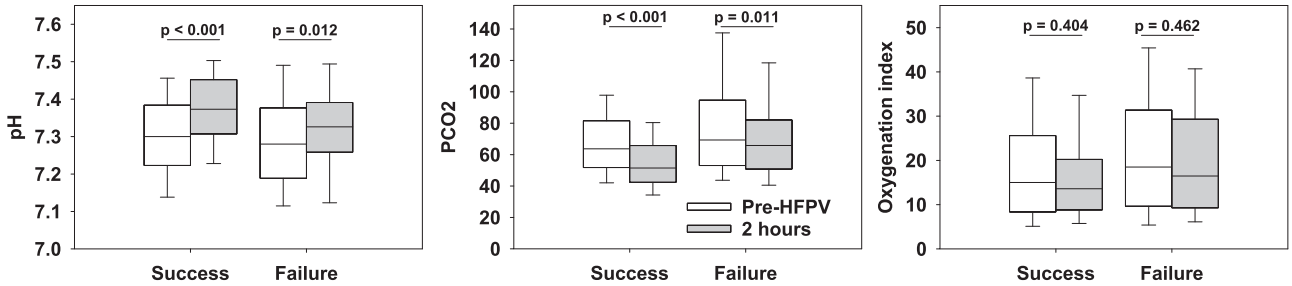

FIGURE 2 Comparisons of pH, PCO_2, and oxygenation index pre-HFPV and 2 h post-HFPV, stratified by HFPV success or failure. *p* Values are the results of signed rank test for paired values. HFPV, high frequency percussive ventilation

ventilation within 2 h of HFPV initiation with lower PIPs and mPaw, compared to those that had failed courses.

HFPV was successful in approximately two-thirds of patient courses in our study. Unlike HFOV which has been associated with unfavorable hemodynamics and use of neuromuscular blockade,[15,16] we did not find increased use of either vasopressor support or neuromuscular blockade with HFPV. This may be due to the fact that HFPV appears to be utilized earlier in refractory ARF than HFOV. In a large multicenter study, HFOV was started at a median OI of 25.7 (IQR: 16.7, 37.3),[17] relative to a pre-HFPV median OI of 16.6 (IQR: 8.6, 26.9) in our cohort. Thus, some of the differences in rates of adverse effects between these modalities may be due to a lower severity of hypoxemia at the time of transition. It is notable that HFOV was the next ventilator used in 31% of subjects who failed HFPV, and that persistent hypoxemia was the most common etiology of HFPV failure. However, it is plausible that the sustained mPaw in HFOV is hemodynamically more toxic than the bi-level ventilation of HFPV. In adults, HFOV was associated with worsening right ventricular function[18] and vasopressor requirements.[15] Thus, HFPV may be a promising alternative ventilator mode for its relative hemodynamic stability, relative to HFOV, even in subjects with significant hypoxemia. Similarly, rates of neuromuscular blockade use were lower in our HFPV cohort than in adult[15] or pediatric[17] HFOV cohorts, which may also be advantageous. A direct comparison of these two salvage modes of ventilation for refractory respiratory failure is warranted, with an assessment of both short-term gas exchange as well as longer term patient-centered outcomes.

When transitioning to HFPV, clinicians used similar PIPs in the first 2 h. However, given the near-universal 1:1 inspiratory or expiratory ratio in HFPV, mPaw increased. Overall, these changes were associated with improved ventilation and more efficient CO_2 removal. Indeed, improved ventilation and pH within 2 h of HFPV were strongly associated with HFPV success, and improved PCO_2 at 2 h associated with more VFDs. The high frequency percussion, designed to remove secretions and airway debris, also improves CO_2 elimination.

A study of HFPV from CHOP in 31 children with ARF,[3] as well as a study of 27 children from Primary Children's Hospital in Salt Lake City,[2] demonstrated improved oxygenation and ventilation 6 h after HFPV initiation. A limitation of both of these studies was the assessment of gas exchange 6 h after transitioning to HFPV, raising the concern that unmeasured factors were responsible for improved gas exchange. In this larger study, we shortened the period of assessment of gas exchange to 2 h after HFPV initiation, limiting the impact of any potential co-interventions.

There are several limitations inherent to a single center, retrospective study. Ventilator management, including HFPV initiation and management, was not protocolized, and was at the discretion of the attending physician. Determination of success versus failure relied upon retrospective chart abstraction by two separate clinicians. Approximately one-third of subjects did not have arterial blood gases, requiring reporting of $PvCO_2$ and OSI. However, we are reassured that conclusions were unchanged when restricted to subjects with arterial blood gases. Finally, this study focused on subjects receiving HFPV, and did not compare HFPV to conventional ventilation or to other modes of ventilation, thereby precluding conclusions regarding HFPV efficacy.

Our study also has several strengths. This is the largest HFPV experience reported in either adults or pediatrics, with detailed description of how an experienced center uses HFPV and selects patients for this modality. The patients were a severely ill cohort, with high PRISM III scores, OIs, and mortality. Salvage therapies for refractory hypercarbia are few and poorly described, making this report a helpful addition to the literature. Finally, although the primary outcome was subjective, definitions of HFPV success and failure were defined a priori and adjudicated by two separate reviewers. The prognostic implications of improved ventilation within 2 h of HFPV initiation were consistent in all analyses, increasing confidence in the accuracy of this effect. Further studies are required to directly compare the utility of this particular nonconventional ventilator with other modalities, and to more precisely identify which patients are good candidates for such a comparison.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Andrew D Butler: conceptualization (equal); data curation (lead); formal analysis (supporting); writing original draft (lead); writing review & editing (equal). Cheryl L Dominick: conceptualization (equal);

data curation (equal); formal analysis (equal); writing review & editing (equal). Nadir Yehya: conceptualization (equal); formal analysis (equal); funding acquisition (lead); methodology (equal); supervision (lead); writing review & editing (equal).

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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