Original Article

The effect of high-frequency oscillatory ventilation or airway pressure release ventilation on children with acute respiratory distress syndrome as a rescue therapy

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Background: To investigate the effects of high-frequency oscillatory ventilation (HFOV) or airway pressure release ventilation (APRV) as a rescue therapy on children with moderate and severe acute respiratory distress syndrome (ARDS).

Methods: We retrospectively enrolled 47 children with ARDS who were transitioned from synchronized intermittent mandatory ventilation (SIMV) to either HFOV or APRV for 48 h or longer after failure of SIMV. The parameters of demographic data, arterial blood gases, ventilator settings, oxygenation index (OI), and PaO_2/FiO_2 (PF) ratio during the first 48 h of HFOV and APRV were recorded.

Results: There was no significant difference between the HFOV and APRV groups with survival rates of 60% and 72.7%, respectively. Compared to pre-transition, the mean airway pressures at 2 and 48 h after transition were higher in both groups ($P<0.01$), and the PF ratio at 2 and 48 h in both modes was significantly improved ($P<0.001$). PF ratio and $PaCO_2$ have significant differences at 48 h between two groups. The OI at 2 h after transition had no improvement in either group and was substantially lower at 48 h relative to the pre-transition level ($P<0.001$) in both groups. At 48 h after the transition to both HFOV and APRV, the survivors had lower mean airway pressures, higher PF ratios, and a lower OIs than non-survivors ($P<0.01$).

Conclusions: There was no significant difference on the survival rates of HFOV and APRV application as a rescue therapy for ARDS, but improved oxygenation at 48 h reliably discriminated survivors from non-survivors in both groups.

Keywords: High-frequency oscillatory ventilation (HFOV); airway pressure release ventilation (APRV); children; acute respiratory distress syndrome (ARDS)

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Introduction

Children with acute respiratory distress syndrome (ARDS) who invasive mechanical ventilation experience high mortality. They are often rescued with modes of nonconventional mechanical ventilation. It includes high-frequency oscillatory ventilation (HFOV) and airway pressure release ventilation (APRV). ARDS is a common critical disease in pediatric intensive care units (PICUs) with a prevalence of 7.6% (1,2). Commonly, the effect of conventional comprehensive therapies, such as synchronized intermittent mandatory ventilation (SIMV), fluid management, and administration of medication, have been unsatisfactory with low oxygenation and high $PaCO_2$ levels, which has resulted in high mortality in critically ill children (3). In theory, as part of a lung protection strategy, HFOV can be used to reduce induced injury (4,5) by delivering small tidal volumes at high rates (3–15 breaths/second) (6,7). HFOV is performed as elective and rescue therapy for ARDS in the PICU. It can optimize alveolar recruitment and lung volume, it can also improve oxygenation through the application of high flow rates and frequencies (900 cycles/minute) with low tidal volumes. A high and persistent medium airway pressure is maintained due to the minimal differences in expiratory and inspiratory pressures.

Some studies have shown that HFOV is effective in treating premature infants or neonates with respiratory failure (8,9). However, in recent years, some researchers, such as Gupta *et al.* (10) and Goffi and Ferguson (11), have presented the opposite viewpoint, finding that HFOV does not reduce mortality compared to ventilation in adults and may in fact be associated with worse outcomes in children.

In recent years, APRV has been considered as an alternate mode for refractory hypoxemia (12). Compared with SIMV, using lower peak pressures and inspiratory flow rates can prolong continuous positive airway pressure to recruit available lung units of varying time constants, and it also uses periodic time-cycled releases to facilitate CO_2 clearance. The experience of using APRV is limited, but some studies suggest potential benefits, such as improved vasopressor requirement, cardiac output, and cardiorespiratory advantages of permissive spontaneous respiration throughout the ventilator cycle. In our department, HFOV and APRV are used as rescue therapy in children with acute respiratory failure after failure of SIMV in lung protection strategies. However, to our best knowledge, no study to support its use has been found (13,14). In this retrospective study, we aim to describe the effects of the application of HFOV and APRV as rescue ventilatory support in children with moderate and severe ARDS. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tp-19-178).

Methods

Design

A retrospective study of children with moderate and severe ARDS in the PICU was conducted from January 2014 to February 2019. Children who had been switched to APRV or HFOV after failure of SIMV were included. The trial was conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of Children's Hospital of Zhejiang University School of Medicine (No. 2020-IRB-048) and informed consent was taken from all the patients.

Patient and data selection

Forty-seven ARDS patients between 1 month and 6 years old were recruited. They were divided into two groups: HFOV (SIMV switched to HFOV) group and APRV (SIMV switched to APRV) group. All children were transitioned from SIMV to either HFOV or APRV for 48 h or longer after failure of SIMV. There was no statistic difference between the two groups in terms of age, sex, body weight, or PRISM (Pediatric Risk of Mortality) III scores. The diagnosis of ARDS was established according to the conference in intensive care medicine (15). The application of HFOV or APRV was performed randomly in cases of failure of SIMV, no improvement in oxygenation, and retention of CO_2. In addition to demographic data, the following items were recorded: arterial blood gases, ventilator settings, oxygenation index (OI), and PaO_2/FiO_2 (PF) ratio during the first 48 h of HFOV and APRV.

SMIV strategy

All patients were managed initially with SIMV using a Dräger Evita 4 ventilator (Drägerwerk AG & Co. KGaA, Lübeck, Germany) in the early stages of ARDS. Initiating conventional ventilation with a minimum of 5 cmH_2O of positive end-expiratory pressure (PEEP) and 6–8 mL/kg of tidal volume and to attempt to reduce FiO_2 to ≤0.6

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is our institutional practice for ARDS. The inability to reduce FiO_2 prompts escalation of PEEP and subsequent repeat efforts to reduce FiO_2, with the goal to maintain peak inspiratory pressures (PIP) <30 cmH_2O, oxygen saturation >88–90%, and permissive hypercapnia up to a $PaCO_2$ of 55–60 mmHg, with maintenance of a pH >7.25–7.30. When patients suffered persistently elevated PIP (≥35 cmH_2O), oxygenation difficulties (inability to decrease FiO_2 to ≤0.60 despite increasing PEEP), or ongoing hypercarbia ($PaCO_2$ ≥80 or pH <7.25) we prompted the consideration of changing the ventilation mode of HFOV or APRV as a rescue therapy.

APRV strategy

APRV would be initiated by selecting a peak pressure (P_{high}) and inspiratory time (T_{high}) to at least match the mean airway pressure (mPaw) being delivered by conventional ventilation, with stepwise increases in mPaw by adjusting P_{high} or T_{high} if we were unable to reduce FiO_2 to ≤0.60. Our practice is setting low pressure (P_{low}) to 0 to facilitate rapid emptying and adjusting expiratory time (T_{low}) to terminate at 1/2–3/4 of peak expiratory flow.

HFOV strategy

Patients were converted to HFOV in cases of failure of CMV through setting the mPaw to at least match that delivered by conventional ventilation, and with mPaw escalation until the FiO_2 could be reduced to under 0.60. The amplitude was set to achieve oscillations visible in the pelvis. We set the initial frequency based on patient weight and age. Specifically, we used the following HFOV settings: a FiO_2 of 0.4–1.0, an oscillatory frequency of 6–12 Hz, an inspiration time of 33% of the respiratory cycle, and a pressure amplitude (ΔP) of 25–50 mbar. The oxygenation goal was oxygen saturation of ≥88% on FiO_2 ≤0.60, and the ventilation goal was $PaCO_2$ ≤60 with a pH ≥7.3. Muscle relaxants were given in combination with a sedative to patients who had acute deterioration of gas exchange during excessive spontaneous activity.

Data collection and definitions

We conducted a detailed retrospective review of all medical records. The review included demographics, admission diagnoses, indications for mechanical ventilation, length of mechanical ventilation, ventilator variables (including duration of APRV and HFOV, blood gas analysis, OI, and ventilator settings), vasopressor use in the first 48 h after transition (from SIMV to HFOV or APRV), and mortality.

The calculated measures of oxygenation were the PF ratio and the OI [(mPaw×FiO_2×100)/PaO_2]. The PF ratio and OI before transition are designated "PF_{pre}" and "OI_{pre}", respectively; the values at 2 and 48 h after transition to HFOV are designated PF_{2h} or PF_{48h} and OI_{2h} or OI_{48h}.

Statistical analysis

Continuous variables were described as the means ± standard deviations when they were normally distributed, and median when they were skewed Categorical variables are reported as frequencies and percentages. Continuous data was compared using Student's *t*-test or the Wilcoxon rank-sum test (16). Categorical data was compared using a two-tailed Fisher's exact test or a Chi square test. P<0.05 was considered as statistically significant. Analyses were performed with SPSS 17.0 (IBM Corporation, New York, NY, USA).

Results

Patient characteristics

Forty-seven patients (26 males, 55%) with moderate and severe ARDS were transitioned from conventional ventilation (SIMV strategy) to either APRV or HFOV during the study period as shown in *Table 1*. The most common diagnoses were viral pneumonia and bacterial pneumonia; 16 and 14 patients with viral or bacterial pneumonia were transitioned to APRV and HFOV, respectively. All patients met the radiographic and oxygenation criteria for ARDS at the time of transition. No significant differences were observed with regard to age, length of SIMV, oxygenation, mPaw, PIP, and $PaCO_2$ between the two groups before transition to APRV or HFOV. Three patients were eventually converted to extracorporeal membrane oxygenation (ECMO), and one patient survived (previously in the HFOV group). Patients with ARDS failed conventional ventilation and transitioned to APRV or HFOV at a median length of 1.9 days (1.94±0.73 days) of SIMV and at a median PIP of 35 cmH_2O (35.26±2.56 cmH_2O) before transitioning to APRV or HFOV (*Table 2*).

The mPaw at 2 h (26.56±1.78 cmH_2O) and at 48 h after transition (25.91±1.64 cmH_2O) was higher in both modes

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Table 1 Diagnosis of patients

Diagnosis	APRV group (SIMV+APRV) (n=25), n (%)	HFOV group (SIMV+HFOV) (n=22), n (%)
Viral pneumonia	10 (40.0)	9 (40.9)
Bacterial pneumonia	6 (24.0)	5 (22.7)
Fungal pneumonia	2 (8.0)	2 (9.1)
Alveolar hemorrhage	1 (4.0)	1 (4.5)
Sepsis	3 (12.0)	4 (18.2)
Other	3 (12.0)	1 (4.5)

P>0.05. There was no statistical difference between the two groups regarding diagnosis. APRV, airway pressure release ventilation; HFOV, high-frequency oscillatory ventilation; SIMV, synchronized intermittent mandatory ventilation.

than the pre-transition value (22.40±1.95, P<0.01). The PF_{2h} and PF_{48h} in both modes were significantly improved compared to pre-transition values (P<0.001). Significant differences were observed in PF_{48h} and $PaCO_2$ at 48 h between the APRV and HFOV groups (P<0.01). The OI_{2h} was not improved in either group (P>0.05), and the OI_{48h} of the APRV and HFOV groups were substantially lower than the OI_{pre} (P<0.001) in both groups. The OI of survivors in both cohorts improved over time.

The overall mortality was 34%, with no significant difference between the APRV and HFOV groups. Three patients (one APRV and two HFOV) transitioned to ECMO at a median of 3.5 [3–8] days after transition to APRV or HFOV and at a median of 6 [4–10] days after starting any mechanical ventilation. And the median OI at the time of ECMO cannulation was 36 [33–67] days. All three ECMO patients were cannulated while on HFOV. Two of these three patients died; the one survivor was cannulated to venovenous ECMO after 3 days of HFOV with a pre-ECMO OI of 38.

Ten of 25 patients (40%) with ARDS who transitioned to APRV died. Six of 22 patients (27%) who transitioned to HFOV died. We found no demographic or physiologic variable was associated with mortality before transition to either APRV or HFOV in the two groups. At 48 h after transition to both APRV and HFOV, the survivors had higher PF ratio, lower mPaw, and lower OI values (*Table 3*) than the non-survivors.

Discussion

In this study, pediatric patients with ARDS who transitioned to either APRV and HFOV had a high mortality rate (40% and 27%, respectively). Although the survival rates of the two groups show no significant difference, but the primary analysis indicates that the HFOV group may have more favorable oxygenation than the APRV group at an early stage. Survival was statistically associated with the improvement in oxygenation variables at 48 h after transition to APRV or HFOV. Pediatric patients failing SIMV transitioned to APRV or HFOV relatively early in the course of respiratory failure, with substantial oxygenation defects. The median mPaw before switching to APRV and HFOV was 22.40±1.95 cmH_2O, which was somewhat lower than the pressures used to determine failure of conventional ventilation in a previous pediatric study (17) in which pediatric patients with respiratory failure were transitioned to HFOV at a median mPaw of 26 cmH_2O. However, the present value is similar to the mPaw of 22 cmH_2O at which 60 pediatric patients with an immunocompromised condition and ARDS were transitioned to HFOV or APRV (18). The relatively early transition may be associated with greater comfort with HFOV or APRV in our institution and an unwillingness to increase the peak inflating pressures of 35 cmH_2O. At 2 and 48 h, the mPaw increased substantially with the improvement in the PF ratio but not in the OI. It suggested the increased alveolar recruitment at the cost of higher mPaw. No significant difference in mortality was observed between the two modes (40% in the APRV cohort and 27% in the HFOV cohort, P=0.542), and mortality was slightly lower than the 56% mortality rate of ARDS patients which was reported in a previous study (19). Patients in our study had well oxygenation, such as a low OI and high P/F, which may explain the lower mortality in our study compared to other previous reported data. Since this paper was a retrospective study, and the application of HFOV and APRV was a rescue therapy, we did not analyze the merely SIMV applied patients.

For patients who transitioned to either APRV or HFOV,

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Table 2 Patient characteristics (n=47)

Variable[a]	All (n=47)	APRV group (SIMV+APRV) (n=25)	HFOV group (SIMV+HFOV) (n=22)	P[b]
Age (M)	10.57±10.15	10.00±9.80	11.23±10.73	0.684
Length of SIMV (d)	1.94±0.73	1.94±0.65	1.93±0.82	0.970
PRISM III scores	22.6±19.3	21.9±20.1	23.6±17.5	0.714
Before switch to APRV or HFOV				
mPaw (cmH_2O)	22.40±1.95	22.16±1.93	22.68±1.99	0.366
P/F_{pre}	131.68±16.05	134.76±12.85	128.18±18.75	0.163
OI_{pre}	24.94±2.84	24.84±2.69	25.06±3.06	0.795
Peak inspiratory pressure	35.26±2.56	35.00±2.52	35.55±2.63	0.472
$PaCO_2$	79.57±14.55	79.84±13.84	79.27±15.65	0.896
Vasopressor infusions				
<2	19 (40%)	10 (40%)	9 (41%)	0.974
≥2	28 (60%)	15 (60%)	13 (59%)	
Neuromuscular blockade	23 (49%)	5 (20%)	18 (82%)	0.000
After 2 h of APRV or HFOV				
mPaw (cmH_2O)	26.56±1.78	26.88±1.76	26.05±1.84	0.754
P/F_{2h}	137.11±15.14	138.12±11.68	135.95±18.54	0.630
OI_{2h}	24.83±2.78	24.62±2.63	25.07±2.99	0.590
$PaCO_2$	73.91±11.58	75.80±12.73	71.77±9.96	0.238
After 48 h of APRV or HFOV				
mPaw (cmH_2O)	25.91±1.64	26.52±1.48	25.23±1.57	0.461
P/F_{48h}	161.47±14.96	155.08±9.92	168.73±16.54	0.002
OI_{48h}	21.90±2.83	22.41±2.90	21.31±2.70	0.188
$PaCO_2$	65.74±8.20	68.72±9.03	62.36±5.59	0.007
Length of APRV or HFOV (d)	7.19±2.16	7.24±2.31	7.14±2.03	0.872
Failure of APRV or HFOV and switch to ECMO	3 (6%)	1 (4%)	2 (9%)	
Mortality (nonsurvivor)	16 (34%)	10 (40%)	6 (27%)	0.542

[a], continuous data are in the form of median ± continuous data are, and categorical data are in the form of n (%). [b], medians are compared using the Student's *t*-test or Wilcoxon rank-sum test for unpaired data. Categorical variables are compared using a continuity correction Chi square test. mPaw, mean airway pressure; OI, oxygenation index; ECMO, extracorporeal membrane oxygenation; APRV, airway pressure release ventilation; HFOV, high-frequency oscillatory ventilation; SIMV, synchronized intermittent mandatory ventilation.

the most useful predictors of mortality were measures of oxygenation at 48 h after transition as a fraction of the pre-transition values, which was reported as the PF_{48h}/PF_{pre} and OI_{48h}/OI_{pre}. In both the APRV and HFOV cohorts, the median OI_{48h} of survivors was nearly 45% lower than the median OI_{pre}, whereas in non-survivors, the OI_{48h} and OI_{pre} were nearly identical (*Table 3*). The discriminating values of PF_{48h}/PF_{pre} and OI_{48h}/OI_{pre} might reflect more highly recruitable lung tissue in the survivors. These patients experienced a much larger increase in the PF ratio at 48 h (>75% increase in the PF ratio on APRV, >90% increase on HFOV) with the increased mPaw than non-survivors.

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Table 3 Characteristics of patients transitioned to APRV (n=25) and HFOV (n=22)

Variable[a]	APRV (n=25)			HFOV (n=22)		
	Survivors (n=15)	Nonsurvivors (n=10)	P[b]	Survivors (n=16)	Nonsurvivors (n=6)	P[b]
Age (M)	10.15±9.46	10.20±10.80	0.915	11.15±10.23	10.65±9.78	0.684
Before switch to APRV or HFOV						
mPaw (cmH_2O)	22.25±1.85	21.98±1.78	0.412	22.56±1.92	22.71±1.95	0.325
P/F_{pre}	133.82±11.78	134.78±12.86	0.176	127.19±17.85	128.21±18.64	0.161
OI_{pre}	24.85±2.85	23.79±2.76	0.683	25.04±3.10	25.12±3.14	0.742
$PaCO_2$	79.76±12.91	79.92±13.82	0.852	79.24±14.82	79.32±15.62	0.814
Lung disease (%)						
Viral pneumonia	4 (26.7)	6 (60.0)	0.247	6 (37.5)	3 (50.0)	0.373
Bacterial pneumonia	4 (26.7)	2 (20.0)		4 (25.0)	1 (16.7)	
Fungal pneumonia	2 (13.3)	0		1 (6.3)	1 (16.7)	
Alveolar hemorrhage	0	1 (10.0)		0	1 (16.7)	
Sepsis	3 (20.0)	0		4 (25)	0	
Other	2 (13.3)	1 (10.0)		1 (6.3)	0	
Vasopressor infusions (%)						
<2	6 (40.0)	4 (40.0)	0.998	5 (31.3)	4 (66.7)	0.178
≥2	9 (60.0)	6 (60.0)		11 (68.8)	2 (33.3)	
After 48 h of APRV or HFOV						
mPaw (cmH_2O)	22.65±1.62	27.42±1.51	0.016	21.73±1.49	28.18±1.59	0.013
PF_{48h}	239.12±7.89	131±8.93	<0.001	243.27±14.36	138.47±16.38	<0.001
PF_{48h}/PF_{pre}	1.82±1.37	0.96±1.18	<0.01	1.92±1.53	1.08±1.02	<0.01
OI_{48h}	13.47±2.05	27.79±1.93	<0.001	12.38±2.23	26.93±1.98	<0.001
OI_{48h}/OI_{pre}	0.54±0.13	1.16±0.97	<0.001	0.47±0.12	1.07±0.61	<0.001
$PaCO_2$	65.13±7.92	68.61±9.12	0.247	59.28±4.91	63.26±5.27	0.254

[a], continuous data are in the form of median ± standard deviation, and categorical data are in the form of n (%). [b], medians are compared using the Student's *t*-test or Wilcoxon rank-sum test for unpaired data. Categorical variables are compared using a Fisher exact test. mPaw, mean airway pressure; OI, oxygenation index; PF, PaO_2/FiO_2; APRV, airway pressure release ventilation; HFOV, high-frequency oscillatory ventilation; SIMV, synchronized intermittent mandatory ventilation.

This result is corroborated by the relative improvements in OI (>45% reduction in OI on APRV, >50% reduction on HFOV). It suggests that survivors with more recruitability can improve their PF ratio at a relatively lower mPaw, in contrast to non survivors. PF_{48h}/PF_{pre} and OI_{48h}/OI_{pre} are also useful early markers to distinguish success or failure of APRV or HFOV. Therefore, this allows more invasive therapies to be instituted earlier in children with ARDS. To early detect the children with ARDS transitioned to either APRV or HFOV who have high risk of mortality will allow more directed use of potentially beneficial treatments, including prone positioning, extracorporeal support, or exogenous surfactant. The earlier transition potential to ECMO may bring benefits as prolonged time on any type of mechanical ventilation pre-ECMO has been related to higher mortality (20-22).

The relationship between the mortality and the improvement in the OI and PF ratio within 48 h after

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transition to APRV or HFOV should be further determined in prospective studies. Recent adult studies showed that the increased mortality (23) or no effect (24) of HFOV compared to conventional ventilation, calling into question the use of early oscillatory ventilation. In our study, children with ARDS were transitioned to APRV or HFOV with higher OIs and lower PF ratios than in either adult HFOV trial, and the two modes were used to "rescue" hypoxemia refractory to conventional ventilation. But given these adult studies results, the current use of HFOV as rescue ventilation seems justified.

This research had some limitations, first, it had a small sample size, and it was a retrospective observational study. Secondly, we designed a short follow-up time. Though the association between survival and improved oxygenation was robust, these results should be determined in a prospective study with larger population.

Conclusions

There was no significant difference in mortality rate between the two groups failing SIMV and transitioning to either APRV or HFOV. Improving the oxygenation at 48 h expressed as PF_{48h}/PF_{pre} and OI_{48h}/OI_{pre} can reliably discriminate survivors from non-survivors. Due to the small sample size, single center and retrospective study, considerably more research is needed before this conclusion can be verified.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The trial was conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of Children's Hospital of Zhejiang University School of Medicine (No. 2020-IRB-048) and informed consent was taken from all the patients.

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