High frequency oscillatory ventilation may not rescue ARDS patients: an observational study

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Abstract

HFOV is a rescue mode of ventilation. Our objective was to assess usage and mortality predictors of HFOV. Observational study of ARDS patients, with data extracted from an ICU database. Analysis was carried out using SPSS version 20.0.

Of 136 ARDS patients, 29.4% (40) were placed on HFOV. Use of HFOV correlated with age (38.7±14.8 vs 49.7±19.4 years, p=0.002, 95% CI 4.2, 17.8) and pulmonary insults (Chi^2 value 44.3, p<0.001). Earlier placement was associated with levels of support on conventional ventilation (PIP - 0.343, p=0.029, PEEP - 0.322, p=0.043, FiO2 - 0.404, p=0.010, tidal volumes - 0.4, p=0.009). ICU mortality was 58.8% (80) with 53% in patients on conventional ventilation and 72.5% (29) in patients on HFOV. Multivariate regression identified APACHE IV (score≤70 OR 0.97, 95% CI 0.96, 0.98, p<0.001) and use of HFOV (OR 2.4, 95% CI 1.05, 5.5, p=0.038) as independent predictors of mortality. Baseline PaO2/FiO2 ratio (p=0.006), concurrent iNO (p=0.001), tidal volumes on conventional ventilation (p=0.016) and improved oxygenation (p=0.001) correlated significantly with survival.

HFOV is associated with increased ICU mortality in patients with ARDS.

Key words: HFOV, ARDS, high frequency oscillatory ventilation, mortality.

Introduction

Adult respiratory distress syndrome (ARDS) is characterized by a profound deterioration in oxygenation following an acute insult that leads to an increase in pulmonary-alveolar capillary permeability and subsequent flooding of alveolar spaces with protein-rich fluid. Mortality is higher in genetically susceptible individuals, older ages and in those who develop non-respiratory organ failure. (1-4) A recent classification system separates ARDS into mild, moderate and severe based on oxygenation defects and a need for positive end-expiratory pressure. Severe ARDS is defined as a PaO2/FiO2<100 with PEEP>5 cmH2O. (5)

The treatment of ARDS is primarily supportive, including optimized mechanical ventilation. Yet positive pressure ventilation, when used at extremes of pulmonary physiology can in itself lead to additional lung injury. (6) Depletion of surfactant can lead to cyclic atelectasis with repeated collapse and opening of the remaining few functional alveoli. This cycling of alveoli opening and closing can lead to activation of neutrophils, promote additional lung injury, and lead to loss of functional residual lung capacity (FRC). One of the more common means of recruiting collapsed alveoli and increasing FRC is to keep a higher mean airway pressure and thereby prevent unstable alveoli from collapsing in expiration. In patients with severe ARDS, holding the lung partially open throughout the respiratory cycle or 'open lung ventilation' is an important approach to

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prevent ventilator-induced lung injury. (7) However when conventional forms of ventilation fail to meet oxygenation or ventilation targets, less conventional or 'rescue' modes are occasionally employed to reduce FiO2 and intrapulmonary shunt. Two commonly used modes are airway pressure release ventilation (APRV) and high frequency oscillatory ventilation (HFOV). Airway pressure release ventilation is a pressure-limited, time-cycled mode of mechanical ventilation that allows a patient unrestricted spontaneous breathing during the application of continuous positive airway pressure. (8) High frequency oscillatory ventilation involves the use of a piston pump-driven diaphragm to deliver small tidal volumes at frequencies between 3 and 15 Hz. (9) In this study we reviewed our experience with rescue ventilatory strategies in a mixed population of medical-surgical patients with ARDS.

Objective

To assess the outcomes of patients with ARDS treated with rescue modes of ventilation: HFOV and APRV.

Materials & Methods

In this observational, cohort study, we extracted data from a prospectively collected ICU database (data collected in real-time) on all patients with ARDS (PaO2/FiO2 ratio ≤300, diffuse alveolar and/or interstitial infiltrates on chest radiograph, decreased lung compliance, no evidence of heart failure and a likely predisposing acute etiology) (5) who were admitted to the surgical and medical intensive care units (14 beds+20 beds) of a tertiary care hospital from 2010-2012. Additional data was collected from respiratory therapy online charting and patient records. The recorded data included patient demographics, etiology of respiratory failure, comorbidities, ventilator settings, and blood gas data from baseline to 24 hours of treatment, usage of rescue ventilation (HFOV and APRV), concomitant use of inhaled nitric oxide (iNO), ventilator dependence, complications associated with usage of rescue ventilation (barotrauma, mucus plugging), failure of rescue ventilation, and ICU mortality (30-day mortality).

All patients were initially treated with a standardized lung protective ventilatory protocol (tidal volumes 4-6 ml/kg body weight, plateau airway pressure <32 cmH2O). Patients who failed conventional ventilation, i.e. patients who remained hypoxemic and required high levels of inspired oxygen, or those who had plateau pressures >35 cmH2O despite 4 ml/kg tidal volumes, were treated with rescue ventilatory strategies and/or iNO. For HFOV, the adult HFOV (model 3100B, SensorMedics, Yorba Linda, CA) was used. There was no standard protocol in place for the initiation, titration, or weaning of HFOV. The study protocol was approved by the institutional Research Advisory Committee (RAC No 2121 143).

Statistical analysis

Analysis was carried out in two prospectively defined steps. Descriptive and frequency data was tabulated with means, SDs, and percentages, as appropriate. The differences between baseline variables in patients on conventional vs rescue ventilation and survivors and non-survivors were explored using one-way analysis of variance (one-way ANOVA), *t* test and Chi^2 tests. Univariate and multivariate logistic regression was used to identify significant characteristics associated with mortality in the ICU. In the second step, patients on HFOV were analyzed for variables associated with mortality using one-way ANOVA for ranks and Spearman's rank correlation coefficient. Statistical analysis was performed using the statistical software package (SPSS, version 20.0). For all analyses, a p value <0.05 was considered statistically significant.

Results

All patients with ARDS

One hundred and thirty-six patients with ARDS were admitted between 2010 and 2012. Sixty-four (47.4%) were female, with a mean age 46.6±19.07 years (range 13, 89). Mean APACHE II and APACHE IV scores were 21.3±8.3 and 83.4±33.8. The mean PaO2/FiO2 ratio at admission was 158±115. Thirty-five patients (25%) were categorized as mild ARDS, 50 (37%) moderate ARDS and 51 (38%) severe ARDS. In 77 (56.6%) patients, ARDS was caused by extrapulmonary insults (pancreatitis, sepsis, shock, blood transfusion) whilst in 59 (43.7%) patients, pulmonary causes of ARDS (pneumonia, alveolar hemorrhage, inflammatory

pneumonitis) were identified. Length of stay in the ICU was 21±22.8 days (range 0.1-151 days). Eighty patients (58.8%) died before ICU discharge, with 54 (40%) patients surviving to day 30.

Univariate analysis identified APACHE II scores (p=0.002), APACHE IV scores (p<0.001) and use of HFOV (p=0.045) as significant predictors of ICU mortality. Stepwise logistic regression identified APACHE IV score (score≤70 OR 0.97, 95% CI 0.96-0.98, p<0.001) and HFOV use (OR 2.4, 95% CI 1.05, 5.5, p=0.038) as independent predictors (**Table 1**).

Use of rescue ventilation

Forty (29.4%) patients were started on rescue modes of ventilation: 37 on HFOV, 3 on APRV. The 3 patients started on APRV were converted to HFOV within 2 hours and are included in the HFOV group. Failure of conventional ventilation was the indication in 24 (60%) patients, whilst 16 (40%) patients were started on HFOV as the initial ventilatory mode. Mean APACHE II score was 21±5.96 with a median PaO2/FiO2 ratio 122±172. Seventeen (42.5%) patients had severe ARDS, 11 (27.5%) moderate and 12 (30%) mild ARDS (**Figure 1**), and 87.5% (35) had received direct pulmonary insults leading to ARDS.

Younger patients (38.7±14.8 years) on HFOV were compared to (49.7±19.4 years) on conventional ventilation, (p=0.002, 95% CI 4.2, 17.8) and those with pulmonary causes of ARDS (Chi^2 value 44.3, p=0.000) were more likely to be given a trial of HFOV. There were no significant differences in APACHE II (p=0.79), APACHE IV (p=0.72) scores or baseline PaO2/FiO2 ratios (p=0.063) between the two groups (**Table 2**).

Ventilator settings immediately prior to rescue ventilation were: FiO2 0.9±0.08 (range 0.6-1.0), tidal volumes 325.7±90 ml, peak inspiratory pressures 35±4 cmH2O and 12±2.5 of PEEP. Rescue ventilation was started after a mean of 95±85.6 hours (range 3-480) from diagnosis of ARDS. HFOV settings were: MAP 32±5.5 cmH2O, frequency 4 (range 3-6) Hz. Concurrent inhaled NO was used in 14 patients, mean doses 20 ppm (range 10-20). Time to start of rescue ventilation correlated significantly with peak inspiratory pressures (-0.343, p=0.029), PEEP (-0.322, p=0.043), FiO2 (-0.404, p=0.010) and tidal volumes (-0.4, p=0.009) on conventional ventilation.

Outcomes on HFOV

Oxygenation improved significantly with HFOV (PaO2 14.3±12.8 vs 12.6±8.4, p=0.03 and PaO2/FiO2 ratios 186.8±27.2 vs 124±37, p=0.002). Patients tolerated HFOV well with complications (barotrauma, hemodynamic instability) in only 4 (10%) patients. In 7 patients (17.5 %), HFOV had to be discontinued due to intolerance from hemodynamic compromise or hypoxemia. Patients received HFOV for a median 9175 hours (range 0.1-38098) with ICU length of stay 26.1±30.6 days (range 0.1-151). The ICU mortality rate was 72.5% (29) and 30-day survival rate was 27.5% (10 patients). Mortality was highest in patients with severe ARDS (89%). In patients on HFOV, higher admission PaO2/FiO2 ratio (p=0.006), use of concurrent iNO (p=0.001), lower tidal volumes on conventional ventilation (p=0.016) and improved oxygenation after 24 hours on HFOV (p=0.001) correlated significantly with survival (**Table 3**).

Discussion

The main finding of this study is the higher mortality seen in patients with ARDS placed on HFOV. In fact placement on HFOV was an independent risk factor for mortality in the intensive care unit. For patients started on HFOV, survival was associated with less severe baseline oxygenation impairment, lower tidal volumes on conventional ventilation and improvements in oxygenation indices on HFOV.

HFOV uses a specifically designed ventilator to deliver a continuous distending airway pressure (mPAW) and an oscillating diaphragm to deliver very small tidal volumes (1-4 ml/kg). Therefore, theoretically, HFOV is the ideal 'lung protective' ventilation strategy since it provides very low pressure swings, thereby minimizing volutrauma and atelecrauma, and a constant distending pressure that maximizes alveolar recruitment.

Findings in relation to other studies

Most evidence supporting HFOV in adult ARDS patients

is derived from case reports, (10-12) observational studies, (9,13,14) and randomized controlled trials that demonstrated improvements in oxygenation on HFOV. In 2004, Mehta et al (14) published the largest series of patients on HFOV. One hundred and fifty six patients with severe ARDS (mean PaO2/FiO2 ratio 91, mean APACHE II score 23.8) and refractory hypoxemia on conventional ventilation were 'rescued' with HFOV. They demonstrated significant improvements in oxygenation that persisted for 72 hours after starting HFOV and reported 61.7% 30-day mortality. In our study, our patients were comparably 'less sick' with a mean APACHE II score 21.3±8.3. Also, HFOV was applied to patients with less severe ARDS with median PaO2/FiO2 ratio 122. Our outcomes however are similar to those reported, with improvements in PaO2/FiO2 ratio at 24 hours and 60% 30-day mortality.

Stronger evidence for an outcome benefit comes from the 2 largest randomized controlled trials comparing HFOV to conventional ventilation. Derdak (15) and Bollen (16) both demonstrated a mortality benefit with HFOV. The Bollen study was prematurely terminated but the Derdak (MOAT) study randomized 75 patients with ARDS (mean APACHE II 22, PaO2/FiO2 ratio 114) to HFOV. They demonstrated 37% mortality in the HFOV group compared to 52% mortality in the control group. Smaller studies by Papazian, (17) Samransamruajkit, (18) Demory, (19) and Mentzelopoulos (20) all confirmed improved oxygenation, mortality and reduced treatment failure in the HFOV groups. A recent meta-analysis by Sud et al (21) reviewed all 6 RCTs and concluded that HFOV improved oxygenation ($p<0.001$), had no adverse effects ($p=0.04$) and reduced mortality compared to conventional ventilation, RR 0.77, $p=0.03$. However all comparisons were made with control groups ventilated with higher tidal volumes (>6-9 ml/kg body weight) and therefore not representative of ARDS mortality with usual lung protective ventilation at tidal volumes 4-6 ml/kg ideal body weight. (22) Conversely two clinical trials were published this year, the OSCAR and OSCILLATE, which showed no benefit and in fact, higher mortality in the HFOV group. The OSCILLATE trial (23) randomized 548 patients to either conventional or HFOV. This trial was stopped prematurely by the data safety management committee when mortality in the HFOV group was disproportionately higher compared to the conventional ventilation arm (RR of death 1.33, $p=0.005$). The OSCAR trial (24) randomized 795 patients to HFOV or usual care. They found no difference in rates of death from any cause between the HFOV and control arms ($p=0.85$). The patients in our sample were similar to patients in these two trials. APACHE II scores and PaO2/FiO2 in the OSCILLATE trial were 29 and 121, in OSCAR 21.8 and 113 compared to 21 and 122 in our study. In our study the mortality rate in patients placed on HFOV was higher than in those whom conventional lung protective ventilation was continued, though our rates overall are higher than both groups.

In our study, most patients in whom HFOV was used had failed conventional ventilation. However a small proportion was placed on HFOV as the preferred mode. In these patients also, the mortality rate was higher than patients on conventional ventilation.

Strengths and limitations

A strength of our study is that the group on conventional ventilation was given tidal volumes consistent with lung protective strategies, i.e. 4-6 ml/kg ideal body weight. This makes our comparisons more meaningful and consistent with the standard of care. Our study stands out from other reports as it accurately reflects intensive care physician practice in ARDS. We found that HFOV was being used in patients with mild and moderate ARDS and in a small number was actually the preferred mode of ventilation over conventional modes. We think this practice was supported by previous evidence that demonstrated no adverse effects and possible survival benefits with early use of HFOV.

A major limitation of our study is that most patients on HFOV in our sample had 'failed' conventional ventilation for refractory hypoxemia and were put on HFOV as a salvage measure. Therefore our high mortality rate may be a reflection purely of patients with non-recruitable lung or the subsequent development of nonpulmonary organ failure. Additionally our conclusions are limited by the small numbers of patients placed on HFOV.

Overall mortality rates in our cohort of ARDS patients are higher than that reported by previous studies. Possible explanations may be the underlying disease processes. Most of our patient pool consists of solid organ or bone marrow transplant patients or those with end stage liver, kidney

diseases or hematologic malignancies. Though the APACHE scoring system captures baseline severity of illness it does not reflect ICU events. One limitation of our study is that we did not measure organ specific failure scores, a comparison of which may explain our disproportionately higher mortality in the ICU and at 30 days.

In conclusion, we have shown that HFOV may not be as ideal a 'rescue' mode as previously thought and that may actually increase mortality as compared to conventional ventilation. Patient baseline oxygenation, concurrent use of inhaled NO and improvement in oxygenation may be used to predict a favorable response if HFOV is used.

Table 1. Variables associated with survival in all patients with ARDS

	Survival (n=56)	Death (n=80)	p value (95% CI)
APACHE II score	18.6	23.1	0.001 (1.8, 7.2)
APACHE IV score	70.1	92.6	0.000 (11.5, 33.3)
HFOV used	11	29	0.042*
iNO+HFOV	0	14	0.010*

Legend: HFOV=high frequency oscillatory ventilation; iNO=inhaled nitric oxide; *=Pearson Chi^2 value

Table 2. Patient characteristics on conventional ventilation compared to HFOV

	Conventional ventilation (n=96)	HFOV (n=40)	p value
Age (years)	49.7	38.7	0.002
APACHE II score	21.4±8.9	21.0±5.9	ns
APACHE IV score	84.1 ±36.7	81.9±23.5	ns
PaO2/FiO2 at admission	124±79.6	122±172	ns
Cause of ARDS			0.000
Pulmonary	24	35	
Extrapulmonary	71	5	
ARDS severity			ns
Mild	23	12	
Moderate	39	11	
Severe	33	17	
Vasopressor or inotrope use (% patients)	43.5%	42.6%	ns
Length of stay	18.7±18.3	26.1±30.6	ns
ICU mortality	51	29	0.043
30-day mortality	51	30	0.021

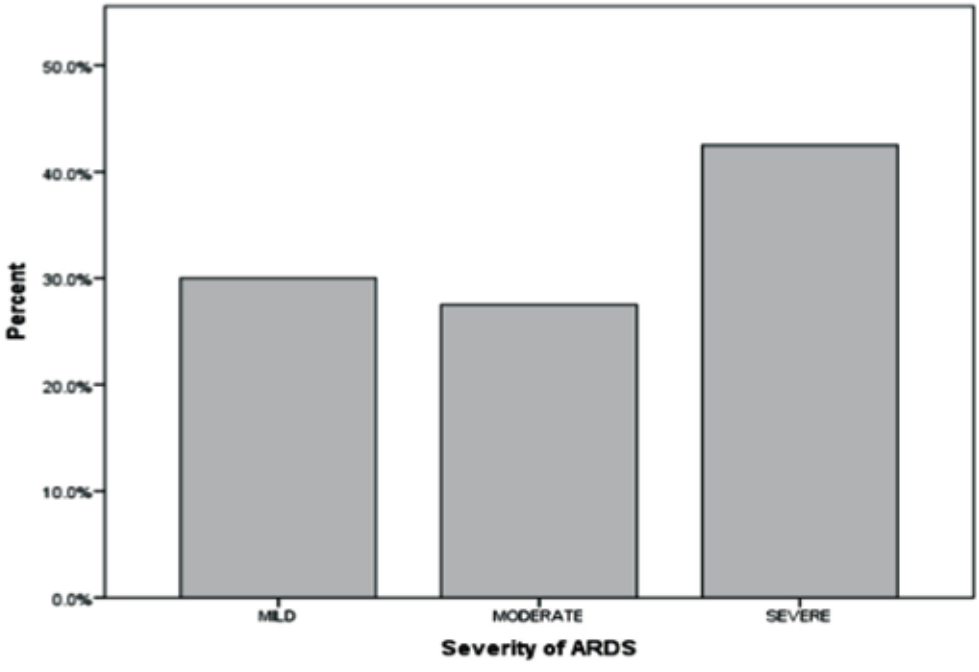
Legend: HFOV=high frequency oscillatory ventilation; PaO2/FiO2=ratio of partial pressure of oxygen in arterial blood by inspired oxygen concentration; ns=not significant

Table 3. Variables associated with ICU survival for patients on HFOV

	ICU death (n=29)	ICU survival (n=11)	p value
Age (years)	36.7±15.2	44±12.7	ns
APACHE II score	21±6.6	20.8±3.6	ns
APACHE IV score	82.3±26.5	80.8±13.7	ns
PaO2/FiO2 ratio at admission	142±99	303±259	0.006
Cause of ARDS			0.004
Pulmonary	25	10	
Extrapulmonary	4	1	
Duration of ventilation prior to HFOV (hours)	91.9±94	104±56	ns
ARDS severity			0.004
Mild	7	5	
Moderate	8	3	
Severe	14	3	
Tidal volumes prior to HFOV (ml)	346±90	271±65	0.016
PIP prior to HFOV (cmH2O)	32±4.9	33.6±4.1	ns
PaO2/FiO2 ratio after 24 hours	100±54.7	168±43.7	0.001
PaO2 after 24 hours (kpascals/mmHg)	9±2.1/68±16	12±1.4/91±10.7	0.000
iNO used	13	0	0.001

Legend: PaO2/FiO2=ratio of partial pressure of oxygen in arterial blood by inspired oxygen concentration; HFOV=high frequency oscillatory ventilation; PIP=peak inspiratory pressure; iNO=inhaled nitric oxide; ns=not significant

Figure 1. Distribution of patients on HFOV by severity of ARDS



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