Use of HFPV for Adults with ARDS: The Protocolized Use of High-Frequency Percussive Ventilation for Adults with Acute Respiratory Failure Treated with Extracorporeal Membrane Oxygenation

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Historically, patients on extracorporeal membrane oxygenation (ECMO) for acute respiratory distress syndrome have received ventilatory "lung rest" with conventional or high-frequency oscillating ventilators. We present a series of adults treated with high-frequency *percussive* ventilation (HFPV) to enhance recovery and recruitment during ECMO. Adult respiratory patients, treated between January 2009 and December 2012 were cared for with a combination of standard ECMO practices and a protocol of recruitment strategies, including HFPV. Data are reported as mean ± standard error of the mean, percentage, or median. Comparisons are made by $\chi 2$ for categorical variables and by t-test and Mann-Whitney test for continuous variables. Significance is noted at the 95% confidence level ($p < 0.05$). There were 39 HFPV patients. They were 39.9±2.2 years of age and had 3.0±0.37 days of mechanical ventilation before the initiation of ECMO. Their pre-ECMO PaO2 to FiO2 ratio (PF ratio) was 52.3±3.0 and their pCO2 was 50.22±2.4. HFPV patients required a mean of 143.1±17.6 hours and a median of 106 hours (range 45.75–350.25) of ECMO support and had a 62% survival to discharge. The post-ECMO PF ratio in the HFPV cohort was 301.8±16.7. A protocolized practice of active recruitment that includes HFPV is associated with reduced duration of ECMO support in adults with respiratory failure. *ASAIO Journal* 2015; 61:345–349.

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Currently, two thirds of adults treated with extracorporeal membrane oxygenation (ECMO) for refractory hypoxemic acute respiratory distress syndrome (ARDS) recover lung function and 60% survive to discharge from the hospital.[1–4] It is common practice that patients receive "lung rest" while being treated with ECMO[4–7] and typically, adults with ARDS require about 10 days of ECMO support to recover lung function.[1,2,4,8,9,29]

There are five basic phases to the successful management of ARDS with ECMO. The first is to gain extracorporeal support and reduce the ventilator's potential for additional injury. Second is to identify the source of inflammation and treat it. Third is to provide general critical care while the compromised lungs recover and fourth is to recruit native lung function sufficient to support the patient. Finally, when the patient can safely sustain their own oxygen delivery requirements, ECMO support is terminated.

We use high-frequency *percussive* ventilation (HFPV) to facilitate alveolar recruitment and to improve native pulmonary function. We report our experience and present the characteristics of several recent cohorts of patients treated with ECMO for respiratory failure. Our observation is that the protocolized use of HFPV with active recruitment strategies may be associated with a reduction in the time ECMO is required for adults with refractory ARDS.

Materials and Methods

Our protocol is to use the lowest level of critical care support to provide adequate oxygen delivery[10] using a full spectrum of ventilator modes, including ARDSnet[11] lung protective strategies, airway pressure release ventilation, and HFPV. We also use adjunctive strategies, including pulmonary artery catheter–directed care, CT imaging to direct therapy, frequent bronchoscopy, aggressive resuscitation, parenteral and inhaled pulmonary vasodilators, targeted diuresis and, when indicated, renal replacement therapy (RRT) to achieve euvolemia.

A protocol[12] guides the increasing intensity of pulmonary support and if, *despite and after* the above measures, a patient cannot achieve a PaO_2/FiO_2 (PF ratio) of >100 on "safe" settings they are considered for ECMO support. If the PF ratio is <80 with an FiO_2 of 1.0, ECMO is initiated.

Once adequate ECMO support is instituted, the HFPV ventilator (Volumetric Diffusive Respirator [VDR-4 critical care ventilator-Percussionaire Corporation, Sandpoint, Idaho]), is set to "lung rest" settings. These settings consist of an FiO_2 of 40%, pulsatile flow rate (inspiratory pressure) in the mid-20 cm of water range, an oscillatory positive end-expiratory pressure (PEEP) of 12 ± 2 cm H_2O, a rate of 15 with an IE ratio of 1:1 and a percussive frequency of 500/minute. All patients on ECMO are maintained with the volumetric diffusive respiration (VDR).

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Further specifics of our routine care have been previously reported.[10,12,28]

Current recommendations by Extracorporeal Life Support Organization (ELSO) for ventilator management on ECMO are: "Reasonable initial ventilator settings during [ECMO] could be decelerating flow (pressure control), a respiratory frequency of 4 to 5 per minute, modest PEEP (*e.g.*, 10 cm H_2O), and low inflation pressure (*e.g.*, 10 cm H_2O above PEEP, or a PIP of 20 cm H_2O). Once patients stabilize and sedation can be lightened, spontaneous ventilation with pressure support ventilation can be considered".[13] The patients in the ELSO registry,[2] the CESAR trial[4], and the REVA trial[29] were treated with a variety of variations on the theme of "lung rest", but none in these cohorts was treated with HFPV.

Patients are evaluated daily for recovery, the timing of which is variable. Evidence of recovery includes a clearing X-ray, decreasing white blood cells and C-reactive protein, weaning of pressors, net negative fluid balance and evidence of intrinsic pulmonary function on daily "step up" ABGs. "Step up" ABG (the Cilley test) shows that the native lung increases oxygenation when the FiO_2 is increased to 100% for a brief period.

The maneuvers of recruitment include, as indicated, diuresis or RRT and positional therapy for parenchymal recruitment, pleural drainage, and other measures to regain thoracic domain, therapeutic bronchoscopy to recruit endobronchial, and percussive ventilation to recruit alveolar spaces. Finally, when safe levels of support (plateau pressure <24 cm H_2O) can achieve ventilation, the VDR provides a combination of increases in the PEEP and delta-P and, if indicated, the initiation of a convective pressure rise (**Figure 1**).

As the patients demonstrate recovery of respiratory function, they are given a "trial off" evaluation of their native pulmonary function without ECMO support. The VDR is set to maintain lung-protective ventilation, and the inspired oxygen is set to 100%. The ECMO circuit gas exchange is then stopped while flows are maintained in the 2–3 liter/minute range. If the patient's hemodynamics are adequate and the PF ratio is >200, theFiO_2 is reduced to 50%. If the PF ratio is >200 on 50%, they are de-cannulated. We do not routinely terminate ECMO on advanced ventilator settings.

Data for the HFPV cohort are collected prospectively and reported to the ELSO Registry. After approval from the ELSO Protocol and Registry Committee with regard to ethical standards, design and the role of informed consent, the ELSO registry[4] was queried for all adult patients who were treated for respiratory failure between January 1, 2009 and December 31, 2012. The data elements studied include patient age, hours of intubation before ECMO (pre-ECMO days), pre-ECMO FiO_2, and PaO_2 (measured in torr and used to derive the pre-ECMO PaO_2 to FiO_2 ratio [pre-ECMO PF ratio]), hours of ECMO support (ECMO hours), type of ventilation while on ECMO (conventional ventilation, high-frequency oscillatory ventilation [HFOV] or "other" which includes HFPV), and survival to discharge. Outliers for the variables of pre-ECMO PF ratio (pre-ECMO PF ratio <10 or >300) and ECMO hours (ECMO hours <24 or > 720) were excluded from the analysis.

Data are managed with SPSS (IBM Corporation, Armonk, New York) and reported as number (n), percentages (%), median, and mean ± standard error of the mean. For continuous variables, paired t-tests are used for comparison of means, Mann-Whitney for comparison of medians, and the Fisher's exact test or χ^2 is used to compare categorical variables. Significance is acknowledged if the criterion of 95% confidence ($p < 0.05$) is met.

Results

The HFPV patients were referred from outside facilities in 91% of cases and 70% required transport with ECMO support. They were 39.3 ± 2.23 years old and 51.3% were male. The causes of ARDS in the HFPV cohort are listed in **Table 1**.

Before initiation of ECMO, patients were ventilated by several modalities, including conventional ventilation with volume and pressure control (CMV and PRVC), airway pressure release ventilation, HFOV, and HFPV. They were uniformly hypoxemic with a PF ratio of 50.3 ± 2.3 despite significant ventilatory and ancillary support. Details of their pre-ECMO

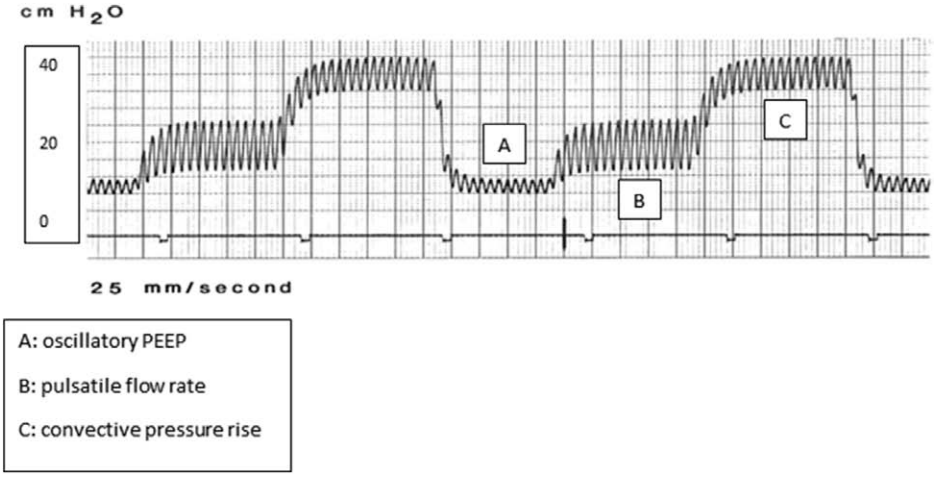

Figure 1. Characteristic waveform of the VDR. A: Oscillatory PEEP. B: Pulsatile flow rate. C: Convective pressure rise. A time:pressure tracing of the Volume Diffusive Respiration (VDR) providing high-frequency *percussive* ventilation (HFPV). Percussive frequency is 500/min. The oscillatory positive end-expiratory pressure (PEEP) is analogous to PEEP. The pulsatile flow rate is the inspiratory pressure and the convective pressure rise is an additional increase in inspiratory pressure that may be added toward the end of each breath.

Table 1. Characteristics of the HFPV Cohort

	Mean	Median	Range
Age (years)	39.3 ± 2.23	36.0	(17–70)
Sex (% male)	51.3		
Weight (kg)	91.7 ± 4.19	91.3	(44.2–155.0)
BMI (kg/m^2)	31.9 ± 1.40	30.3	(17.2–52.8)
Primary diagnosis	n	(%)	
Pneumonia	23	59	
Obstetric ARDS	1	2.5	
Other ARDS	9	23.1	
Trauma	3	7.7	
Other*	3	7.7	

*Includes malaria, pulmonary alveolar proteinosis, and polymyositis. n = 39
ARDS, acute respiratory distress syndrome; BMI, body mass index.

respiratory status are listed in **Table 2**.Twenty-seven patients recovered to wean from ECMO (69%) and 24 patients survived to discharge (62%). Details of their ECMO care are listed in **Table 3** and post-ECMO respiratory characteristics are shown in **Table 4**. Survivors spent 143.1 ± 17.6 hours on ECMO (median 106.0 hours, range 45.8–350.3 hours) and had a post-ECMO PF ratio of 301.4 ± 17.3 on an FiO_2 of 46.0 ± 1.7.

The cause of death for those who died on ECMO was bleeding in 4, overwhelming sepsis in 3, cerebral ischemia in 3, cerebral hemorrhage in 1, and cardiac arrest in 1. Three patients died after weaning from ECMO, two of profound neurologic injury, and one of inanition. No patient in the HFPV cohort died of ARDS.

The HFPV patients spent 17.6 ± 2.8 days on the ventilator after weaning from ECMO, 18.3 ± 2.9 days in the intensive care unit and 37.3 ± 4.3 days in the hospital before discharge. All of the HFPV survivors ultimately returned to their homes neurologically intact.

Table 5 lists characteristics of four modern cohorts of adults treated with ECMO for respiratory failure. In comparison with the ELSO cohort, the HFPV cohort is no different with regard to pre-ECMO days of mechanical ventilation or survival but has significantly lower pre-ECMO PF ratios ($p < 0.001$) and ECMO hours ($p < 0.001$) by t-test for comparison of means and Mann-Whitney test for comparison of medians ($p = 0.043$ and 0.44, respectively). The duration of ECMO was between 9 and 11 days in the ELSO, CESAR, and REVA cohorts and 6 days for the HFPV cohort.

Table 2. Pre-ECMO Respiratory Characteristics of the HFPV Cohort

	Mean	Median	Range
Pre-ECMO days of MV	3.0 ± 0.37	2.5	(1.0–11.0)
FiO_2 (%)	99.7 ± 0.26	100.0	(90.0–100.0)
PIP (cmH_2O)	39.3 ± 2.02	38.0	(18.0–70.0)
PEEP (cmH_2O)	15.8 ± 0.86	18.0	(5.0–22.0)
pH	7.26 ± 0.02	7.26	(6.91–7.48)
pCO_2 (torr)	50.22 ± 2.42	47.0	(23.0–89.0)
pO_2 (torr)	48.7 ± 2.2	51.5	(23.0–74.0)
HCO_3 (mmol/L)	21.95 ± 0.92	21.0	(12.0–32.0)
SaO_2 (%)	76.9 ± 3.2	84.0	(36.0–94.0)
Pre-ECMO PF ratio	50.3 ± 2.3	53.0	(23.0–89.0)

MV, mechanical ventilation; PEEP, positive end-expiratory pressure.

Table 3. ECMO Characteristics of the HFPV Cohort

	mean	median	range
FiO_2 (%) at 24 hours of ECMO	49.7 ± 2.9	40.0	(30.0–65.0)
PIP (cm H_2O) at 24 hours of ECMO	27.7 ± 0.93	26.0	(18.0–40.0)
PEEP (cm H_2O) at 24 hours of ECMO	13.9 ± 0.50	12.0	(10.0–20.0)
Pump flow (L/min) at 24 hours of ECMO	4.48 ± 0.12	4.5	(2.65–5.90)
Hours of ECMO	143.1 ± 17.6	106.0	(45.75–350.25)

PEEP, positive end-expiratory pressure.

Discussion

HFPV delivered by the VDR is different from either conventional pressure control ventilation (PCV, PRVC) or HFOV. The VDR uses a time-regulated convective component and a superimposed subtidal volume percussive component of about 30 ml. A unique sliding piston called a Phasitron regulates both the percussive and convective components. This provides a combination of diffusive intrapulmonary gas mixing because of the percussive feature with an intermittent scheduled convective tidal exchange of variable length and profile.[14–17] This differs significantly from the high mean airway pressures (MAPs) and oscillation of HFOV and has been shown to be safe in children and burned and injured adults.[17–27] The ability of this ventilator to mobilize secretions and recruit alveoli, coupled with minimizing regional over-distention and ventilator induced lung injury make it an optimal choice for ventilating patients with injured and variably compliant lungs.

The baseline pressure is termed the oscillatory PEEP, peak inspiratory pressure is called the pulsatile flow rate, and an optional additional positive pressure component is named the convective pressure rise (Figure1). Ventilation, achieved by increasing minute ventilation, is facilitated by adjusting the pressure variation, reducing the percussive rate, decreasing the

Table 4. Post-ECMO Respiratory Characteristics of the HFPV Cohort

	Mean	Median	Range
Percent of HFPV patients with tracheostomy	39% (n = 16)		
FiO_2 (%)	46.0 ± 1.4	45.0	(30.0–65.0)
Pulsatile flow rate (cm H_2O)	28.92 ± 0.96	28.0	(18.0–36)
Oscillatory PEEP (cm H_2O)	13.00 ± 0.43	12.0	(8.0–16)
Convective pressure rise (cm H_2O)	36.67 ± 0.54	36.0	(32.0–40.0)
Percussive rate (per min)	503.64 ± 6.25	500	(405–600)
MAP (cm H_2O)	22.13 ± 0.64	22.0	(17.0–29.0)
pH	7.42 ± 0.01	7.42	(7.26–7.52
pCO_2 (torr)	42.9 ± 1.9	40.5	(32–76)
pO_2 (torr)	135.2 ± 7.2	133	(133–205)
HCO_3 (mmol/L)	26.8 ± 0.7	27	(21–33)
SaO_2 (%)	98.1 ± 0.23	98	(95–99)
Post-ECMO PF ratio (at decannulation)	273.38 ± 23.73	257.5	(126.0–382.2)
Post-ECMO PF ratio (best in first 24 hours)	301.04 ± 17.3	292.0	(123–498)

HFPV, high-frequency percussive ventilation; MAP, mean airway pressure; PEEP, positive end-expiratory pressure.

Table 5. Four Modern Cohorts of ECMO for Respiratory Failure in Adults

	Age	Pre-ECMO days of MV	Pre-ECMO PF ratio	ECMO hours	MV days	ICU days	Survival
CESAR	39.9 ± 13.4	1.46	75.9	216	n/a	24 (13–41)	63%
REVA	42 ± 13	2	63	264	25 (14–40)	32 (15–56)	64%
ELSO	43.3 ± 15.7	4.75	79.4	215	19.8 (6–143)	n/a	59%
HFPV	36.8 ± 14.8	3.1	54.5	143	25.5 (5–87)	27 (6–97)	62%

CESAR, Conventional ventilation or ECMO for Severe Adult Respiratory failure; ELSO, Extracorporeal Life Support Organization; HFPV, high-frequency percussive ventilation; MV, mechanical ventilation; REVA, RéseauÉducatif des VillesAriane.

I:E ratio, or allowing for a cuff leak. Oxygenation is enhanced by increasing the percussive rate, the FiO_2, or the MAP. The MAP can be raised by increasing the oscillatory PEEP or the pulsatile flow rate, increasing the inspiratory time or by adding a convective pressure rise. The convective pressure rise and cuff leak are also helpful for secretion mobilization and clearance.

Several mechanisms are postulated to explain how the VDR ventilator works. The high-frequency percussions function by a combination of longitudinal (Taylor) dispersion, the generation of asymmetric velocity profiles within the tracheobronchial tree, and molecular diffusion at the alveolar level. The convective tidal breaths generate a more traditional bulk flow physiology and truly ventilate in excess of dead space. The roles of pendelluft and cardiogenic mixing contribute regionally throughout the lung and are more pronounced in less compliant segments.[14–17]The net result is a gentle ventilatory cycle that is supplemented by a high-velocity percussive component. This mobilizes secretions and recruits compromised areas of atelectasis without over-distending and injuring more compliant areas of the lung.

Because of the ease with which HFPV recruits functional residual capacity and mobilizes endobronchial debris, it first became popular for adults with inhalation injury and for pediatric reactive airway disease and cystic fibrosis. In animal models, HFPV has been shown to improve both oxygenation and ventilation while decreasing both the histologic and chemical evidence of inflammation and secondary lung injury.[18–20]Retrospective human studies have demonstrated improved oxygen index, PaO_2:FiO_2 ratios, ventilation, and compliance relative to conventional ventilation modes.[21–24] Prospective, randomized trials in human have demonstrated that HFPV results in lower peak airway pressures, higher PaO_2:FiO_2 ratios, and a reduction for the need for "rescue" modalities relative to low tidal volume ventilation.[25,26]

Application of the VDR to the dense consolidation, tenacious secretions, and tracheobronchial hemorrhage of adults requiring ECMO for refractory hypoxemic ARDS was a natural extension of our experiences with ARDS in pediatric, septic, burn, and trauma patients. We remain conservative regarding iatrogenic injury to the lung during the phase of active inflammation, but once that phase has passed and there are physiologic and radiographic signs of recovery we initiate genuine efforts to recruit functional residual capacity and increase lung function. The VDR ventilator is a key element in our strategy of recruitment.

This report is essentially a case series and comparison with other modern cohorts and has several limitations. Several aspects of our practice besides our choice of ventilator may differ from those in the centers included in the ELSO, CESAR, and REVA cohorts. In addition to our use of HFPV, our use of CT imaging, pulmonary artery catheter–directed interventions, frequent bronchoscopy, positional therapy, diuresis and RRT, and active recruitment once recovery is secure may have affected our time on ECMO relative to the other cohorts. Nevertheless, the only demonstrable therapeutic difference between the patients cared for in our center and the other modern cohorts is with the use of HFPV while on ECMO.

The low pre-ECMO PF ratio, implying more severe ARDS in the HFPV cohort, may be due to the fact that 70% of our patients were too compromised to move and required ECMO for transport to our facility. This is an unusually high percentage compared with the ECMO community in general and is a marker of our practice of treating patients otherwise too compromised to make it to an ECMO center.

Because ECMO for adults with ARDS has become more widely accepted, it is incumbent upon us, the ECMO community, to maintain a continuous evaluation of our practices with the goal of providing the most efficacious and efficient care. A reduction of the time necessary to provide extracorporeal support with comparable outcomes may reduce the cost and the risk of ECMO while liberating limited resources to serve other patients requiring extracorporeal support. We first recognized that our time on ECMO was less than the norm as many reports following the H1N1 pandemic became available. We noted that our ECMO times were significantly shorter for the subgroup of adults with ARDS caused by H1N1 pneumonia.[28] That observation led to both the more intentional use of recruitment techniques and this report of a more generalized group of ARDS patients.

Conclusion

In summary, reducing time on ECMO for adults with refractory hypoxemic ARDS without compromising overall outcomes has merit. ECMO care, although effective, is accompanied by significant costs and risks and represents a limited clinical resource. By reducing the time an individual requires ECMO support, these risks and costs are decreased and the potential conflict of more patients than available circuits is also lessened. This report suggests that the time required for adults with ARDS to recover and wean from ECMO may be reduced by the protocolized use of HFPV and an active strategy of lung recruitment. It will require prospective and randomized evaluation to address these possibilities independently and conclusively. We present a cohort of adults treated with ECMO, HFPV, and recruitment strategies who had comparable survival and weaned from ECMO in two thirds of the time of the international benchmarks represented by the ELSO

registry for respiratory failure and the cohorts of the CESAR and REVA trials.

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