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High frequency percussive ventilation and bronchoscopy during extracorporeal life support in children

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Abstract

Variables affecting duration of pediatric extracorporeal life support (ECLS) are poorly defined. Prior analyses suggested increased mortality risk with prolonged ECLS. Lung recruitment strategies with improved secretion mobilization may shorten ECLS duration. High frequency percussive ventilation (HFPV) has been used, predominantly in inhalational injury, as a mode of ventilation to improve secretion clearance. We describe the application of HFPV and therapeutic bronchoscopies in pediatric ECLS, and evaluate outcomes with a same-center historical control population. After May, 2011, all children (n = 14) on ECLS were managed with HFPV during extracorporeal support (HFPV cohort). This group's demographics and outcomes were compared to ECLS patients in our unit immediately prior to the utilization of HFPV (pre-HFPV cohort, n = 22). The HFPV and pre-HFPV cohorts had similar demographics and utilization of venoarterial ECLS. In univariate analysis, the HFPV group underwent more bronchoscopies and experienced more ECLS-free days (days alive and off ECLS) at 30 and 60 days. In multivariate analysis, use of HFPV was independently associated with ECLS-free days. We conclude that use of HFPV and bronchoscopies during ECLS for respiratory failure was associated with an increase in ECLS-free days, and that this association should be prospectively evaluated.

Introduction

Mortality from pediatric respiratory failure treated with extracorporeal life support (ECLS) remains high at 43%.[1] Studies evaluating predictors of mortality for pediatric ECLS for respiratory failure have identified patient diagnosis,[1-3] presence of co-morbidities,[1] pre-ECLS oxygenation,[1, 2, 4, 5] and pre-ECLS length of mechanical ventilation[1-3, 5, 6] as associated with higher mortality. Stratified analyses have suggested that the effect on mortality is not apparent until pre-ECLS mechanical ventilation exceeds 14 days.[1, 5]

Prolonged ECLS is associated with poor outcomes.[2, 3, 7, 8] Analysis of 1489 pediatric patients with pneumonia in the Extracorporeal Life Support Organization (ELSO) registry between 1985 and 2010 showed predicted mortality decreasing by 1.3% daily until day 14, after which mortality increased by 1.8% per day.[2] Separately, ELSO patients between 1993 and 2007 receiving > 21 days of ECLS for respiratory failure had higher mortality (62%) relative to those on for ≤ 14 days (39%).[8] Time on ECLS may be either a marker for illness severity, reversibility of underlying disease, or recoverability of cardiopulmonary function. It is unknown whether therapies aimed at decreasing time on ECLS will improve outcomes.

Pulmonary management during ECLS may affect duration of support. Traditional "rest settings" may risk unnecessary atelectasis and derecruitment in the attempt to limit ventilator induced lung injury during ECLS. A single neonatal study suggests that higher levels of positive end-expiratory pressure during ECLS may shorten the duration of extracorporeal support,[9] but otherwise there is no literature to guide ventilator management. Additionally, flexible bronchoscopy on ECLS[10-12] has been reported to improve pulmonary function leading to reductions of ECLS flows.[11, 12] However, the optimal role of bronchoscopy during ECLS is undefined.

Since May, 2011, our pediatric intensive care unit (PICU) has approached ECLS for respiratory failure with a focus on improved secretion clearance and early recruitment. To this end, the initial and predominant mode of ventilation utilized on ECLS was changed to high frequency percussive ventilation (HFPV), which has been well-described in inhalational injury for its ability to safely oxygenate and ventilate, with continuous pneumatically-powered high frequency percussions to facilitate clearance of airway debris.[13-16] An increase in therapeutic bronchoscopies was also instituted. The purpose of this study is to compare the outcomes of the patients who underwent HFPV and therapeutic bronchoscopies while on ECLS with a same-center control population immediately prior to these interventions. We hypothesized that use of HFPV and bronchoscopies were associated with shorter ECLS runs and improved outcomes.

Methods

Design, patient population, and data collection

This study was approved by the Children's Hospital of Philadelphia Institutional Review Board, and the requirement for informed consent was waived. Since January 1, 2008, our PICU has maintained a prospectively collected database of all consecutive patients placed on ECLS. Data elements include demographics, mechanical ventilation settings pre- and post-ECLS, gas exchange parameters pre- and post-ECLS, use of additional extracorporeal therapies, complications on ECLS, and outcomes of ECLS. Our PICU is a 55 bed unit with medical and surgical pediatric patients; primary cardiac disease, including congenital heart disease and myocarditis, are cared for in a separate cardiac unit. CHOP has been an ECLS center since 1990, and has over 1000 ECLS runs between the neonatal, cardiac, and pediatric intensive care units.

All children in our PICU placed on ECLS between January, 2008 and May, 2013 were eligible for inclusion. After May, 2011, all children received HFPV while on ECLS as their main mode of mechanical ventilation. We designated all consecutive ECLS patients between May, 2011 and May, 2013 as the "HFPV cohort," with the population immediately preceding (January, 2008 to April, 2011) serving as the historical comparison group ("pre-HFPV" cohort). We excluded patients placed on ECLS during cardiopulmonary resuscitation (ECLS-CPR) as factors affecting ECLS-CPR survival may differ substantially from other pediatric indications.

ECLS strategy

The decision to initiate ECLS was left to the attending physician. For venovenous (VV) cannulation, the initial 3 patients (January to November, 2008) were cannulated using an OriGen (OriGen Biomedical, Austin, Texas) dual lumen catheter in the right internal jugular vein, with a single patient requiring an additional femoral venous cannula. All subsequent VV cannulations used the Avalon (Avalon Laboratories LLC, Rancho Dominguez, California) bicaval dual lumen catheters placed under echocardiographic guidance in the right internal jugular vein. Venoarterial (VA) access involved the right internal jugular vein and carotid artery with ligation of the artery without subsequent reconstruction. We exclusively used the Quadrox oxygenator (Maquet, Germany) and the S5 roller pump system (Sorin, Germany) throughout the study period. For both VV and VA ECLS, pump flows were weaned as oxygenation improved, and patients were liberated from extracorporeal support if radiographs were improving, mean arterial pressures were stable on minimal vasopressors, and patients were able to maintain $Sa_{O_2} > 94\%$ and $Scv_{O_2} > 70\%$ with ventilator peak inspiratory pressures ≤ 30 cmH_2O and $F_{IO_2} \leq 0.5$. Daily multidisciplinary ECLS rounds were instituted in January, 2008, with involvement of the critical

care attending, the ECLS specialist, bedside nurse, respiratory therapist, and one of two senior PICU physicians specializing in ECLS.

The pre-HFPV cohort was ventilated with the Evita XL (Dräger, Lübeck, Germany) in pressure preset mode during ECLS, with typical initial settings of a peak inflating pressure < 25 cmH_2O, an inspiratory:expiratory ratio of 1:2, and a positive end-expiratory pressure (PEEP) between 8 and 12 cmH_2O.

HFPV strategy

After May, 2011, HFPV using the VDR-4 ventilator (Pecussionaire, Sandpoint, Idaho) was the initial and main mode of mechanical ventilation during ECLS. Use of HFPV and therapeutic flexible bronchoscopies were part of a quality improvement strategy of aggressive lung recruitment during ECLS focusing on improved secretion mobilization. After initiation of ECLS, patients were transitioned to HFPV and maintained on it until secretion burden was deemed minimal. Typical HFPV starting settings used were a high frequency percussive rate of 600 beats/minute superimposed on a conventional rate of 10-20 breaths/minute, a peak pressure < 25 cmH_2O, an inspiratory:expiratory ratio of 1:1, and PEEP set between 8 and 12 cmH_2O. Inadequate aeration on radiograph prompted an increase in end-expiratory pressure. Persistent minimal secretions prompted discontinuation of HFPV. All patients after May, 2011, underwent an initial bronchoscopy with the goal of mucus removal, with subsequent bronchoscopies being guided by the findings of the initial bronchoscopy, with additional bronchoscopies performed until minimal mucus plugs were encountered. All adjustments to HFPV settings, the decision to discontinue HFPV, and the frequency of bronchoscopies were determined during daily multidisciplinary ECLS rounds.

Definitions and equations

Immunocompromised conditions were defined as the presence of a congenital immunodeficiency, or as the presence of an oncologic, rheumatologic, or transplant status receiving active immunosuppressive chemotherapy, as per prior studies on immunocompromised children. [17, 18] Renal failure was defined as requiring renal replacement therapy. Liver dysfunction was defined as transaminitis and bilirubin > 3-fold above normal limit. ECLS-free days are a composite endpoint of ECLS duration and survivial status, and were defined as the number of days a patient is alive and off of ECLS at 30 and 60 days.

We used a previously described vasopressor score[19-21]: dopamine dose (µg/kg/min) x 1 + dobutamine (µg/kg/min) x 1 + epinephrine (µg/kg/min) x 100 + norepinephrine (µg/kg/min) x 100 + phenylephrine (µg/kg/min) x 100 + milrinone (µg/kg/min) x 10. The measure of oxygenation used in the study is the oxygenation index (OI), calculated as the (mean airway pressure [mPaw] x FIO_2 x 100/ PaO_2).

Statistical analysis

Continuous data are reported as median [25th and 75th percentiles], and categorical data are reported as numbers (%). Univariate comparisons of continuous variables were performed using the Wilcoxon rank sum test, and categorical variables were compared using the Fisher exact test. Multivariate (backward and forward selection) regression was used to identify factors independently associated with ECLS-free days at 30 and 60 days. *A priori* variables included ventilator days pre-ECLS, use of VA-ECLS, presence of an immunocompromised condition, kidney failure requiring dialysis, liver dysfunction, number of bronchoscopies on ECLS, and use of HFPV on ECLS. Additional terms which were considered were Pediatric Risk of Mortality

(PRISM) III, pH pre-ECLS, OI pre-ECLS, and vasopressor score pre-ECLS, all of which were co-linear with the use of VA-ECLS, and so were not modeled. Iterative addition of these terms to the final model did not improve overall fit as assessed by adjusted R^2. Significance is defined as $p < 0.05$ for all analyses. Calculations were performed in Stata 10.0 (StataCorp LP, College Station, Texas).

Results

Study population

Thirty-nine patients have been supported with ECLS in our PICU between January, 2008 and May, 2013. Three patients were excluded from further analysis as they were placed on ECLS during CPR, leaving 14 patients receiving HFPV (HFPV cohort) after May, 2011, and 22 comprising the pre-HFPV cohort (Table 1). No statistically significant differences were noted between the HFPV and pre-HFPV cohorts with respect to demographics, diagnoses, PRISM III, and percentage of patients with immunocompromised conditions, renal failure requiring dialysis, or liver dysfunction. Two patients, one in each cohort, had undergone allogenic hematopoietic stem cell transplant. The length of mechanical ventilation, pH and OI pre-ECLS, maximum vasopressor scores in the 24 hours pre-ECLS, and utilization of VA-ECLS were also similar. All patients in both cohorts received less than 14 days of mechanical ventilation pre-ECLS. Ventilator settings on conventional pressure preset ventilation (pre-HFPV) and HFPV (HFPV cohort) were similar between the cohorts, with the exception of the conventional rate, which was higher in the HFPV cohort (Table 1).

Outcomes

Patients in the HFPV cohort received a median 6 days [IQR 5, 9] of HFPV during ECLS and underwent more therapeutic bronchoscopies (2 [1, 3] in HFPV cohort versus 1 [0, 2] in pre-HFPV, $p = 0.019$). Compared to the pre-HFPV cohort, patients in the HFPV cohort had more days alive and off of ECLS at 30 and 60 days (Table 2), and did not experience increased air leaks, inability to wean vasopressors, or other complications. In stepwise multivariate regression analysis, use of HFPV was independently associated with more ECLS-free days at both 30 and 60 days (Table 3). Use of VA-ECLS and kidney failure requiring dialysis were both associated with fewer ECLS-free days at both 30 and 60 days, and the presence of an immunocompromised condition was associated with fewer ECLS-free days only at 60 days.

Discussion

The use of HFPV and therapeutic bronchoscopies during ECLS was associated with more days alive and off ECLS at 30 and 60 days. HFPV utilization was independently associated with ECLS-free days in multivariate analysis. These results suggest that the mode of mechanical ventilation and the pulmonary toilet strategy are modifiable factors that can affect duration of extracorporeal support.

Higher mPaw leading to improved lung recruitment does not explain the difference between the HFPV and pre-HFPV cohorts, as the mPaw, peak pressures, and PEEP used in the first 72 hours of ECLS were similar (Table 1). Improved secretion clearance in the HFPV cohort may have led to improved pulmonary compliance at similar mPaw, leading to faster recovery and shorter ECLS durations. HFPV is also thought to improve alveolar recruitment because of more sustained mPaw throughout the ventilator cycle, as well as maintaining airway patency

during expiratory oscillations.[22, 23] It is also possible that the combination of HFPV and bronchoscopic secretion removal resulted in more rapid radiographic improvement, thus enabling earlier trials off of ECLS.

Since the interventions were delivered simultaneously as a bundled strategy aimed at improved secretion clearance, our study does not permit a robust delineation of whether the increase in ECLS-free days was associated with more bronchoscopies, with the use of HFPV, or a synergy of both interventions. In stepwise multivariate analysis, number of bronchoscopies was not retained as a significant independent predictor of ECLS-free days, and the calculated β coefficient was negative, likely because longer ECLS exposure implied worse lung disease and prompted more bronchoscopies. Furthermore, the HFPV cohort experienced a median of only 1 extra bronchoscopy relative to the pre-HFPV cohort (Table 2), making this intervention unlikely to explain the increased ECLS-free days. HFPV use was retained as a significant predictor in multivariate analysis, but the possibility of confounding cannot be excluded. Of note, the increased number of ECLS-free days at 30 (12.5 more ECLS-free days) and at 60 days (31 more ECLS-free days) in the HFPV cohort is substantially larger than the shortened time on ECLS in those who survived to decannulation (4 fewer days, not-significant), suggesting that the increase in ECLS-free days is driven mostly by the lower mortality in the HFPV cohort.

The use of HFPV and bronchoscopies on ECLS in our institution occurred without noted complications, including no hemodynamic instability, no dangerous pulmonary bleeding, and no increased incidence of pneumothorax. This is consistent with the reported safety and possible efficacy of therapeutic bronchoscopies while on ECLS.[10-12]

The different indications for ECLS may also be relevant as to which population would most benefit from HFPV and bronchoscopic secretion removal. In both pre-HFPV and HFPV

cohorts the most common indications for ECLS were aspiration or infectious pneumonias (20 of 22 in pre-HFPV, and 12 of 14 in HFPV cohort, Table 1). This type of direct lung injury may be particularly benefited by our targeted secretion removal strategy to shorten time on ECLS.

There are several limitations to our study. The small sample size, retrospective nature, and use of historical control preclude firm conclusions regarding the benefits of bronchoscopies and HFPV, and these results should be considered preliminary and hypothesis-generating. To minimize confounding from temporal drift and improvements of care with time in our same-center historical control, we limited our pre-HFPV cohort to our prospectively collected database starting in 2008. No statistically significant differences were noted between the cohorts with respect to many variables associated with mortality on ECLS, including age, diagnoses, co-morbidities, immunocompromised status, pre-ECLS length of mechanical ventilation, pre-ECLS OI, pre-ECLS vasopressor score, and use of VA-ECLS. Similarly, processes of care were similar between cohorts, as the ECLS cannulation technique, the circuit (including oxygenator and rollerhead pump), and multidisciplinary rounding format did not change during the course of the study. The single center nature of our study, while addressing some of the above concerns, may limit the generalizability of the results.

Finally, our primary outcome of ECLS-free days is a composite endpoint incorporating both mortality and ECLS duration. Mortality is not significantly different between the cohorts; however, our study is underpowered to detect differences in mortality, and we do not conclude from these preliminary data that there is an association between HFPV and bronchoscopy with improved survival. Reporting ECLS duration alone risks assigning patients who die early during the ECLS run as having "shorter" (and therefore favorable) times on ECLS, and so is an inappropriate metric for efficacy of interventions. Much like the use of ventilator-free days in

the acute respiratory distress syndrome literature, ECLS-free days is a meaningful, patient-centered outcome.

Furthermore, it is possible that shortening the duration of ECLS is not beneficial despite the association of increased mortality with extracorporeal support over 14 days.[2] Arguably, ECLS is providing adequate gas exchange while limiting toxicity associated with mechanical ventilation, and shortening duration of ECLS may not necessarily lead to better outcomes. We feel this possibility is less likely given the trends towards improved ventilator-free days and survival in the HFPV cohort, meaning that the shortened duration of ECLS in our HFPV cohort was not accompanied by increased length of mechanical ventilation or increased mortality.

In conclusion, the use of HFPV and therapeutic bronchoscopies was associated with more days alive and off ECLS at 30 and 60 days, and the use of HFPV was independently associated with ECLS-free days. These findings suggest that HFPV use during ECLS may be beneficial; further prospective multi-institutional investigations are warranted.

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Table 1. Population characteristics.

Variable[a]	Pre-HFPV (n = 22)	HFPV (n = 14)	*p* value[b]
Age (years)	6.4 [1, 10.4]	7.3 [2, 15]	0.455
PRISM III at 24 hr	11.5 [5, 16]	8.5 [3, 18]	0.745
Male/female	12/10	10/4	0.485
Race			
White	11 (50%)	8 (57%)	
Black	7 (32%)	5 (36%)	0.698
Asian	2 (9%)	1 (7%)	
Other	2 (9%)	0 (0%)	
Length of ventilation pre-ECLS (days)	3 [1, 6]	1 [0, 5]	0.373
OI pre-ECLS	48.6 [42.6, 60.7]	52.9 [36.4, 58.4]	1
pH pre-ECLS	7.29 [7.21, 7.33]	7.21 [7.17, 7.33]	0.246
Vasopressor score 24h pre-ECLS	12.5 [2, 25]	18 [8, 28]	0.269
Co-morbidities			
Immunocompromised	7 (32%)	3 (21%)	0.706
AKI requiring dialysis	5 (23%)	4 (29%)	0.712
Liver dysfunction	7 (32%)	4 (29%)	1
Mode of ECLS			
VV	15 (68%)	8 (57%)	0.277
VA	5 (23%)	6 (43%)	
VV → VA	2 (9%)	0 (0%)	
Diagnosis			
Viral pneumonia	10 (45%)	6 (43%)	
Bacterial pneumonia	6 (27%)	3 (21%)	
Fungal pneumonia	2 (9%)	0 0%)	0.556
Aspiration pneumonia	2 (9%)	3 (21%)	
Air leak syndrome	0 (0%)	1 (7%)	
Sepsis	2 (9%)	1 (7%)	
Ventilator settings during ECLS			
mPaw (cmH_2O)	13 [11, 18]	15.5 [12, 18]	0.504
Peak pressure (cmH_2O)	26 [22, 30]	25.5 [22, 28]	0.485
PEEP (cmH_2O)	10 [9, 12]	10 [10, 12]	0.863
Conventional rate (bpm)	10 [10, 12]	15 [15, 20]	<0.001
High frequency rate (bpm)	-	600 [600, 600]	-

HFPV, high frequency percussive ventilation; PRISM, Pediatric Risk of Mortality; ECLS, extracorporeal life support; OI, oxygenation index; AKI, acute kidney injury; VV, venovenous;

VA, venoarterial; mPaw, mean airway pressure; PEEP, positive end-expiratory pressure; bpm, breaths/minute

[a] Continuous data are in the form of median [interquartile range], and categorical are in the form of n (%).

[b] Medians are compared using the Wilcoxon rank sum test, and categorical variables compared using a Fisher exact test.

Table 2. Effects of HFPV on clinical outcomes.

Variable[a]	Pre-HFPV (n = 22)	HFPV (n = 14)	*p* value[b]
Days of HFPV	-	6 [5, 9]	-
Bronchoscopies per patient	1 [0, 2]	2 [1, 3]	0.019
Frequency of bronchoscopies (days on ECLS between bronchoscopies)	11.8 [5.5, 13.5]	6 [4.3, 8.4]	0.060
Vasopressor score 24h post-ECLS	3.5 [0, 5]	0 [0, 5]	0.428
Developed air leak on ECLS	7 (32%)	3 (21%)	0.706
ECLS-free days			
30 days	7 [0, 17]	19.5 [13, 22]	0.042
60 days	18.5 [0, 47]	49.5 [43, 52]	0.035
Ventilator-free days			
30 days	0 [0, 0]	0 [0, 5]	0.518
60 days	0 [0, 24]	21 [0, 35]	0.092
Days on ECLS (all patients)	13 [11, 19]	10.5 [8, 16]	0.389
Survival to decannulation	14 (64%)	12 (86%)	0.255
Days on ECLS	13 [11, 19] (n = 14)	9 [7, 14] (n = 12)	0.315
Survival to hospital discharge	11 (50%)	11 (79%)	0.160

HFPV, high frequency percussive ventilation; ECLS, extracorporeal life support

[a] Continuous data are in the form of median [interquartile range], and categorical are in the form of n (%).

[b] Medians are compared using the Wilcoxon rank sum test, and categorical variables compared using a Fisher exact test.

Table 3. Stepwise multivariate linear regression for ECLS-free days at 30 and 60 days.

Outcome	Variable	Effect on ECLS-free days	95% CI	*p* value
ECLS-free days at 30 days	Use of HFPV (yes)	9.2	3.8 to 14.6	0.002
	Use of venoarterial ECLS (yes)	-8.6	-14.4 to -2.8	0.005
	AKI requiring dialysis	-6.8	-13.0 to -0.6	0.034
ECLS-free days at 60 days	Use of HFPV (yes)	21.3	9.2 to 33.3	0.001
	Use of venoarterial ECLS (yes)	-19.8	-32.8 to -6.8	0.004
	AKI requiring dialysis	-15.0	-28.7 to -1.4	0.032
	Immunocompromised condition (yes)	-14.2	-27.4 to -1.0	0.036

HFPV, high frequency percussive ventilation; ECLS, extracorporeal life support; AKI, acute kidney injury