Flexible Bronchoscopy in Pediatric Venovenous Extracorporeal Membrane Oxygenation

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BACKGROUND: Pediatric patients with ARDS will on occasion need venovenous extracorporeal membrane oxygenation (VV-ECMO) for organ support. As these patients recover, they may benefit from lung recruitment maneuvers including flexible bronchoscopy (FB). The objective of this study was to assess the clinical course of patients who underwent FB while on VV-ECMO for ARDS. METHODS: This was a secondary analysis of a retrospective multi-center cohort at 10 United States pediatric academic quaternary care centers. Data were collected on 204 subjects age 14 d–18 y on VV-ECMO. RESULTS: 271 FBs were performed on 129 (63%) subjects. Pre-FB tidal volume was 1.8 mL/kg compared to 2.22 mL/kg following FB ($P = .007$). Dynamic compliance also improved from pre-FB to post-FB (2.23 vs 3.04 mL/cm H_2O, $P = .005$). There was a low incidence of complications following FB (3.1%). Subjects in the FB group had fewer ECMO-free days (EFDs) (17.9 vs 22.1 d, $P < .001$), fewer ventilator-free days (VFDs) (40.0 vs 46.5 d, $P = .001$), and longer ICU length of stay (LOS) (18 vs 32 d, $P < .001$). Subjects in the early versus late FB group had more EFDs (19.4 vs 15.2 d, $P = .003$), more VFDs (43.0 vs 34.0 d, $P = .004$), and shorter ICU LOS (27.5 vs 35.5 d, $P = .045$). Mortality in the subjects who had at least one FB was 27.1% compared to 40% in the subjects who did not have a FB while on VV-ECMO ($P = .057$). CONCLUSIONS: FB can be performed on patients while anticoagulated on VV-ECMO with a low incidence of complications. FB may be beneficial especially when performed early in the course of VV-ECMO. *Key words: flexible bronchoscopy; venovenous ECMO; pediatric ARDS; mechanical ventilation; pulmonary clearance; lung recruitment.* [Respir Care 2022;67(6):688–693. © 2022 Daedalus Enterprises]

Introduction

Pediatric ARDS is a common but challenging disease to treat in the pediatric ICU. The overall goals of treating a patient with pediatric ARDS are to improve gas exchange while limiting ventilator-induced lung injury.[1] Patients are often transitioned to venovenous extracorporeal membrane oxygenation (VV-ECMO) when there is a concern the required ventilator support is injurious or unable to provide adequate gas exchange. For children receiving VV-ECMO support, flexible bronchoscopy (FB) can be helpful as diagnostic and/or therapeutic tool. FB can aid in the removal of airway debris such as mucus, purulent material, blood, or foreign bodies that contributed to the respiratory failure.[2]

Jenks et al[3] reported that 55% of pediatric centers and 81% of mixed pediatric and adult centers use FB as part of

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their lung recruitment strategy for patients on ECMO. At present, limited evidence exists to make recommendations on the practice of FB. There are few single-center studies that describe complications or examine the effect of bronchoscopy on lung mechanics for subjects requiring VV-ECMO.[2-6] Developing an understanding of clinical course is important because there are potential risks to doing FB in patients being anticoagulated on ECMO. This includes desaturation, fever, bleeding, pneumothorax, need for increased respiratory or ECMO support, and endotracheal tube dislodgement.[5,7]

The primary aims of this study were to describe the clinical impact of FB on subjects receiving VV-ECMO. In addition, to assess lung mechanics and complications surrounding FB performed on pediatric subjects requiring VV-ECMO. The secondary aim was to look at the outcomes associated with subjects that had at least one FB. We hypothesized the use of FB in subjects on VV-ECMO would be well tolerated and associated with higher tidal volumes and improved lung compliance.

Methods

This is a secondary analysis of data gathered from a prior study describing mechanical ventilator practices for children on VV-ECMO; the methods are described in more detail in the primary manuscript.[8] This is a retrospective multi-center cohort study conducted at 10 pediatric academic quaternary care centers in the United States. Each center is a member of the Pediatric ECMO subgroup of the Pediatric Acute Lung Injury and Sepsis Investigators Network and the Extracorporeal Life Support Organization. Institutional review board (IRB) approval was completed locally or at the lead institution (Indiana University). The most recent IRB approval for this manuscript is through the Spectrum Health IRB, approval number 2017–011. Need for informed consent was waived. All subjects were

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QUICK LOOK

Current knowledge

Pediatric patients with ARDS may be treated with venovenous extracorporeal membrane oxygenation (VV-ECMO) for managing hypoxia and hypercarbia while allowing the lungs to recover and prevent ventilator-induced lung injury. Flexible bronchoscopy (FB) can be a useful tool both diagnostically and therapeutically for patients with severe ARDS. Single-center reports show minimal complications occurring with FB while on VV-ECMO.

What this paper contributes to our knowledge

This is the largest and only multi-institutional study describing the use, complications, and lung mechanics surrounding FB on VV-ECMO. There was a low incidence of complications, improved lung mechanics, and early versus late bronchoscopy should be strongly considered.

managed based on the local hospital protocols or at the clinician's discretion.

The electronic medical records were reviewed for children age 14 d–18 y cannulated for VV-ECMO from 2011–2016. Those not meeting the following exclusion criteria were included in the study. Exclusion criteria were (1) ECMO as a bridge to lung transplant, (2) diagnosis of asthma as the primary cause of acute respiratory failure, (3) patients with cyanotic congenital heart disease (unrepaired cyanotic congenital heart disease or single-ventricle physiology), or (4) preexisting chronic respiratory failure (defined as ventilator dependence, positive-pressure ventilation, or home O_2 not for obstructive sleep apnea).

Data were collected and entered into REDCap, a HIPAA-compliant online data entry web site (Vanderbilt University, Nashville, Tennessee).[9] Pre-ECMO data collected included demographics, Pediatric Pulmonary Rescue With Extracorporeal Membrane Oxygenation Prediction (PPREP) variables[10] and Pediatric Risk Estimate Score for Children Using Extracorporeal Respiratory Support (Ped-RESCUERS) variables,[11] ventilator settings, blood gas values, and time prior to initiating ECMO. ECMO settings, including blood flow, sweep, and F_{IO_2}, were recorded for the first 7 d on ECMO, using values recorded closest to 8:00 AM. The pre-ECMO ventilator settings are the settings documented closest to the 8:00 AM before cannulation.

Bronchoscopy data for the first 5 bronchoscopies were collected. These data included indication, timing of bronchoscopy, ventilator and ECMO settings closest to 8:00 AM before and after bronchoscopy, lung compliance pre- and post-bronchoscopy, and blood products administered in the

Table 1.   Demographics

Variable	No FB (n = 75)	FB (n = 129)	P
Age	2.3 [0.5, 9.9]	4.2 [1.2, 12.5]	.044
Gender (male)	38 (50.7)	55 (42.6)	.27
Comorbidities			
Pre-ECMO cardiac arrest	6 (8.0)	14 (10.9)	.51
Prematurity	13 (17.3)	32 (24.8)	.22
Genetic disorder	12 (16.0)	7 (5.4)	.01
Congenital heart disease	10 (13.3)	8 (6.2)	.08
Asthma	12 (16.0)	20 (15.5)	.93
Developmental delay	10 (13.3)	9 (7.0)	.13
Chronic lung disease	3 (4.0)	11 (8.5)	.22
Malignancy	11 (14.7)	14 (10.9)	.42
Stem cell transplant	5 (6.7)	4 (3.1)	.29*
Calculated OI	47.8 ± 20.8	49.0 ± 22.8	.73
PPREP score	3 [1.0, 8.0]	3.0 [1.0, 5.0]	.49
Ped-RESCUERS score	−0.4 ± 0.7	−0.5 ± 0.7	.80

Normally distributed numeric data are expressed as mean ± SD; non-normally distributed numeric data are expressed as median [25th, 75th percentile]; categorical data are expressed as n (%). (*) denotes Fisher exact test.
FB = flexible bronchoscopy
ECMO = extracorporeal membrane oxygenation
OI = oxygenation index
PPREP = Pediatric Pulmonary Rescue With Extracorporeal Membrane Oxygenation Prediction
Ped-RESCUERS = Pediatric Risk Estimate Score for Children Using Extracorporeal Respiratory Support

Table 2.   Indications for Flexible Bronchoscopy

	FB (no = 271)
Diagnostic versus therapeutic	
Diagnostic	64 (23.6)
Therapeutic	129 (47.6)
Diagnostic and therapeutic	78 (28.8)
Therapeutic types	
Pulmonary toilet	129 (47.6)
Lung re-expansion	18 (6.6)
Chest radiograph findings	37 (13.7)
Mucous plugging	58 (21.4)
Bleeding	18 (6.6)
Routine	0 (0)
Other	22 (8.1)

Data are expressed as no. (%).
FB = flexible bronchoscopy

24 h following bronchoscopy. More specifically, compliance data were collected for subjects on conventional ventilation. Tidal volume, peak inspiratory pressure, and PEEP were collected at 8 AM prior to bronchoscopy and 8 AM following bronchoscopy. Compliance was then calculated from these variables. Outcome data as it related to FB included ECMO-free days (EFDs) at 28 d, ventilator-free days (VFDs) at 90 d, ICU LOS, and mortality. We further looked at the data based on timing of bronchoscopy, dividing the groups into early and late FB. Early FB was defined as bronchoscopy done during the first 3 d of being on ECMO.

Demographics and outcomes that are numeric in nature are summarized as mean ± SD or median (25th, 75th percentile), depending on normality assumption being met. Categorical variables are summarized as frequency (percent). Comparisons were performed between FB and no-FB grouping. To compare the numeric demographics between these groups, a 2-sample independent t test or Wilcoxon rank-sum was performed based on normality assumptions being met. Comparisons between the groups and categorical data were analyzed using chi-square or Fisher exact test if the expected cell counts were below 5 in > 20% of the cells. Comparisons on outcomes were accessed using the groupings no FB, early FB, and late FB. The numeric outcomes (EFD at 28 d, VFD at 60 d, ICU LOS) were analyzed using Kruskal-Wallis analysis, and if that test was significant, a post hoc analysis using

Wilcoxon rank-sum and a Bonferroni correction was utilized to access which groups had a difference. The categorical outcome mortality was analyzed using chi-square analysis. All analyses were completed using SAS (SAS version 7.1, SAS Institute, Cary, North Carolina).

Results

Demographics

There were 204 subjects included from the 10 institutions that required VV-ECMO. Table 1 shows the basic demographics of the subjects, comparing the no-FB group to the FB group. The median age for all subjects was 3.6 y (interquartile range [IQR] 1.1–12.1) with 53% females. The etiologies of respiratory failure were viral infection (other than respiratory syncytial virus) (29%), other causes (28%), respiratory syncytial virus infection (17%), bacterial pneumonia (13%), aspiration (6%), sepsis (4%), fungal pneumonia (2%), and pertussis (1%). The median peak oxygenation index (OI) was 47 (IQR 35–62). The median length of ECMO support was 7.9 d (IQR 4.9–14). Overall survival was 68%. The most common causes of death were multiorgan failure (30%), bleeding complications (30%), and refractory lung disease (25%). Median duration of ECMO was 190 h (IQR 117–337). Tracheostomy was placed after ECMO in 22 subjects (11%), and 14 subjects (7%) were discharged on home mechanical ventilation.

Indications and Timing of Flexible Bronchoscopy

Of these 204 subjects, 129 subjects (63%) had at least one FB. There was a total of 271 FBs performed on these 129 subjects. Table 2 shows the indication for brochoscopy

Table 3. Diagnostic Versus Therapeutic Flexible Bronchoscopy

Diagnostic Versus Therapeutic	Early FB (n = 166)	Late FB (n = 99)
Diagnostic	40 (24.1)	22 (22.2)
Therapeutic	72 (43.4)	55 (55.6)
Diagnostic and therapeutic	54 (32.5)	22 (22.2)

Data are expressed as n (%).
FB = flexible bronchoscopy

and therapeutic types. The indication for bronchoscopy was for diagnostic purposes 64 (23.6%), pulmonary clearance 129 (47.6%), or both 78 (28.8%). The median time to the first bronchoscopy was 68 h (IQR 25–119). We divided the subjects into early FB (first 72 h) and late FB (beyond 72 h). There was no difference in indication based on timing of FB. Table 3 shows timing for FB based on indication.

Complications

Complications reported included 4/129 subjects (3.1% [95% CI 1.0–7.8]) with pulmonary hemorrhage following FB; one of those subjects was admitted with pulmonary hemorrhage, and one subject had a tension hemothorax approximately 6–8 h following bronchoscopy. No pneumothorax was reported following FB (0% [95% CI 0–2.8]). In the primary manuscript,[8] 27 subjects had a documented pneumothorax. Five (18.5%) of these subjects did not have an FB. The pneumothorax was documented prior to bronchoscopy in 9 (33.3%) of the subjects, and in 13 (48.1%) of the subjects the pneumothorax was documented at 1–5 d following bronchoscopy.

Lung Mechanics

The predominate mode of ventilation for subjects in the FB group was conventional ventilation (71.7%). Other modes of ventilation at the time of bronchoscopy included airway pressure release ventilation 17.3%, high-frequency oscillatory ventilation 3.1%, high-frequency pulsatile ventilation 4.7%, and 2.4% was extubated. Calculated dynamic compliance was only done for subjects on conventional ventilation. The measured tidal volume per kilogram of weight prior to FB was 1.8 mL/kg versus 2.22 mL/kg recorded after FB (P = .007). Calculated dynamic compliance prior to FB was 2.23 mL/cm H_2O compared to 3.04 mL/cm H_2O following FB (P = .005). These data were collected at 8 AM prior to the FB and again at 8 AM following the FB.

Outcomes

There was no difference in the severity of illness between the subjects in the FB group compared to those in the no-bronchoscopy group based on calculated OI, PPREP scores, and Ped-RESCUERS scores (Table 1).

Table 4 shows patient outcomes. Subjects in the FB group had fewer EFDs (17.9 vs 22.1 d, P < .001), fewer VFD (40.0 vs 46.5 d, P = .001), and longer ICU LOS (18 vs 32 d, P < .001).

Subjects in the early versus late-FB group had more EFDs at 28 d (19.4 vs 15.2 d, P = .003), more VFDs at 60 d (43.0 vs 34.0 d, P = .004), and shorter ICU LOS (27.5 vs 35.5 d, P = .045).

There was no difference in ECMO sweep, blood flow settings, or mean airway pressure before and after FB.

Mortality in the FB group was 27% versus 40% in the no FB; P = .057. Mortality in the early-FB group was 23.5% compared to 31.6% in the late-FB group; P = .11.

A logistic regression model examining the association between clinical variables and mortality (Y or N) did not show age, genetic disease, comorbidities, or timing (late vs early) of the bronchoscopy to be predictive of mortality.

Discussion

This is the largest and only multi-center study to date that describes the use of FB for pediatric subjects on VV-ECMO. These data examine ventilator and ECMO

Table 4. Patient Outcomes

Variable	No FB (n = 75)	Early FB (n = 68)	Late FB (n = 57)	P
EFD at 28 d	22.1 [19.5, 24.0]	19.4 [13.9, 22.8]	15.2 [9.0, 19.1]	< .001
VFD at 60 d	46.5 [37.5, 52.0]	43.0 [30.0, 50.0]	34.0 [23.0, 41.0]	< .001
LOS	18.0 [13.0, 32.0]	27.5 [17.0, 41.0]	35.5 [24.5, 47.0]	< .001
Mortality	30 (40.0)	16 (23.5)	18 (31.6)	.11

EFD, VFD, and LOS data are expressed as median [25th, 75th percentile]. Mortality is expressed as n (%).
FB = flexible bronchoscopy
EFD = extracorporeal membrane oxygenation–free d at 28 d
VFD = ventilator-free d at 60 d
LOS = length of stay (in ICU)

variables before and after FB and describe clinical outcomes for children who have had an FB while on ECMO. The data on complications specifically pulmonary hemorrhage and pneumothorax from this study are consistent with prior literature published on FB performed for subjects on VV-ECMO.[3-6] Despite the risks of bleeding due to anticoagulation, there were only 4 subjects (1.5%) documented as having a pulmonary hemorrhage following FB. In one of these subjects, the admitting diagnosis was pulmonary hemorrhage. Another subject was noted to have a tension hemothorax about 8 h following FB, and there were no other details recorded. Despite this subject having a significant complication, this accounted for 0.4% of the FBs performed in this study. The incidence of pulmonary hemorrhage in our subjects was less than that seen for pediatric patients on VV-ECMO reported in the Extracorporeal Life Support Organization database, 8.1%.[12]

No subjects were reported to have a pneumothorax in association with FB. However, 27 subjects in the cohort had a new pneumothorax while on ECMO reported in the primary manuscript, but remote from bronchoscopy.[8] Thirteen of these, which is 4.5% of the total FBs, were documented at 1–5 d following FB. It is not possible to definitively say whether this was associated with the FB. In previously reported literature, the incidence of pneumothorax following FB is variable from 0.3–3.4%.[13,14] Literature specifically describing the incidence of pneumothorax in pediatric ARDS patients following implementation of lung-protective ventilation strategies was still 17%, improved from 55%.[15]

These data show the overall incidence of complications, specifically pneumothorax and pulmonary hemorrhage, following FB is low. This can help clinicians to weigh the risk and benefits of FB to be performed on patients who are anticoagulated on ECMO. It can also be used to better inform families of the risk to the patient.

Subjects who underwent FB had fewer EFDs, VFDs, and longer ICU LOS. It is possible that bronchoscopy may lead to morbidity and more ventilator days ECMO days and longer LOS due to complications. However, complications are rare, and both tidal volume and compliance were shown here to improve after bronchoscopy. It is possible that patients with more severe lung injury and longer runs of ECMO are more likely to undergo bronchoscopy.

Our data demonstrate subjects in the early-FB group had more EFD, VFD, and had shorter ICU LOS compared to the subjects in the late-FB group. Logistic regression revealed no differences in mortality between late- and early bronchoscopy subjects after accounting for clinical variables such as age and comorbidities.

Diagnostic bronchoscopy obtained early may identify a source or cause of the patient's respiratory failure, leading to a change in treatment that could ultimately help the patient improve more quickly.[2] Early bronchoscopy may also improve lung compliance and mucociliary clearance, allowing for lung recovery while avoiding increased inflammation from atelectrauma and barotrauma from high ventilator settings.[16-18] Bronchoscopy can remove larger mucous plugs that may be preventing lung recruitment and ultimately weaning from VV-ECMO.[19] Yehya et al[20] found that subjects with pediatric ARDS supported with ECMO had increased survival and decreased length of time on ECMO when treated with high-frequency pulsatile ventilation and bronchoscopy combined. They suggest improving secretion clearance may lead to improved lung compliance resulting in faster recovery and shorter duration of ECMO.

Strengths of our study include it being multi-institutional and the largest study to describe bronchoscopy practices for pediatric subjects on VV-ECMO. There are several limitations. First is its retrospective design– it lacks specific details that could have only been collected prospectively. Data were only collected on the first 5 bronchoscopies; collecting data on all bronchoscopies could have provided further data. We were unable to compare lung compliance of subjects not on conventional ventilation both before and after FB. The time between FB and collecting the post-FB data was variable; collecting data at multiple time points following bronchoscopy could have been more useful. We did not assess for ventilator-associated pneumonia as a possible complication of longer time on ECMO and possibly the reason for FB late in ECMO.

Conclusions

FB for children supported with VV-ECMO can be done with a low incidence of complications. Lung mechanics including tidal volumes and lung compliance were improved in subjects following FB. The association between FB and longer duration of ECMO needs examination by prospective design. The improved survival in the cohort and overall safety of the procedure in this multi-center study indicate that the procedure should be considered when appropriate in patients on VV-ECMO.

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