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All authors have no conflict of interest to declare.

No funding to declare for this study

Key words: Bundle, ARDS, ECMO, children

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ABSTRACT:

Objective: Defining the best ventilatory settings under ECMO remains a challenging question. Despite a well-defined ARDS treatment before ECMO initiation, there is no recommendation on how to ventilate a patient under ECMO for P-ARDS. Only a few descriptive studies are available on ventilatory settings during respiratory ECMO. We aim at evaluating the usefulness of a protective ventilation bundle under ECMO and its capacity to reduce the ventilatory pressure in our ECMO center.

Methods: We performed a monocentric retrospective study from January 2007 to December 2018. All children aged from 1 month to 18 years old and requiring an extracorporeal membrane oxygenation for a refractory acute respiratory distress syndrome were included. A protective mechanical ventilation under ECMO bundle has been developed in 2014. We compare the period 1 (before 2014) to the period 2 (after 2014).

Results: Eighty-three patient had been included during the study. We reported a significant increase of PEEP and mean pressure respectively at day 3, day 7 and day 14 of ECMO during the period 2. Conversely, the driving pressure were significantly lower in the period 2 at day 3 (p: 0.009), day 7 (p:0.001) and day 14 (p: 0.001). We also shown a strong increase in the use of prone positioning during ECMO in the period 2 (p: 0.01). There was no significant effect of our bundle on the length of mechanical ventilation, of hospitalization and on the survival rate.

Conclusion: The implementation of a protective mechanical ventilation bundle during ECMO is usefulness to apply for lower ventilatory pressure and higher use of prone positioning. Nonetheless, the lack of power of our study prevents us from showing its efficacy on outcome criteria.

Introduction

The treatment of pediatric acute respiratory distress syndrome (P-ARDS) is nowadays well-defined and allows a strong improvement of the outcome (1). Indeed, the use of protective mechanical ventilation (2–4) has a major role in this treatment and leads to a significant rise of survival rate (5). However, a small proportion of P-ARDS still evolves into a refractory distress syndrome. Despite all the available therapies (6–8), the mortality rate of this most severe patients remains above 30% (9) and some patients require an extracorporeal membrane oxygenation (ECMO) as a salvage therapy. The use of extracorporeal membrane oxygenation is not free of severe adverse events as hemorrhage, thrombosis or nosocomial infection (10) and recent data have failed to show that early ECMO in severe ARDS is not most efficient than isolated protective mechanical ventilation and all the adjunctive therapies (11). During the last decade, the main part of the literature was focused on ECMO indication and side effects without studying factors associated with pulmonary function recovery. This complex phenomenon depends on various parameter such as fluid overload (12,13), evolution of lung compliance (14), the use of steroids (15). Among all the parameters involve into the pulmonary function recovery, the type and settings of the mechanical ventilation during ECMO to avoid ventilation induced lung injury remain unclear. Only few data are available in adults (16–18) and identified that a higher positive end expiratory pressure during the first three days of ECMO is associated with a better outcome. Only one study is available in children (19) We decided to create a protective mechanical ventilation bundle since 2014 (table 1) and the implementation of our mobile ECMO team (20) resulting in a significant rise of P-ARDS under ECMO in our unit. In this study, we aim at comparing the "before 2014 period" to the "after 2014 period" and look for variations of the mechanical ventilation after the implementation of a "protective ventilation under ECMO" bundle in our unit.

Methods:

We performed a retrospective monocentric study from January 2007 to December 2018 in the high-volume extracorporeal membrane oxygenation center of Armand-Trousseau hospital, Paris, France.

Patients

All children aged from 1 month to 18 years old and requiring an extracorporeal membrane oxygenation for a refractory acute respiratory distress syndrome were included.

Data collection:

In both period, data collected were age, gender, weight, ARDS etiology and severity score (PIM II and PELOD score, vasoactive score, PaO_2/FiO_2 a ratio, oxygenation index and the oxygenation saturation score) (21). We look for pre-ECMO data's such as the use of prone positioning, nitric oxide, exogenous surfactant, neuromuscular blockers, and high frequency oscillation. We also collected for all patients the use of steroids, of cross-sectional imaging, the length of invasive mechanical ventilation, intensive care hospitalization.

We also gathered ECMO flow (ml/min), ventilatory settings at day 3, 7 and 14 of ECMO (PEEP, mean pressure, inspiratory pressure, driving pressure, tidal volume and respiratory rate). The driving pressure was defined by P_{max} - PEEP when the patient was in a barometric setting (5) and P_{plat} – PEEP when the patient was in a volumetric setting (6).

Finally, we look for outcomes criterion: survival rate, duration of ECMO, invasive mechanical ventilation and hospitalization. We also look for the use of prone positioning and steroids during ECMO run.

We decided to create a protective mechanical ventilation bundle (Table 1) since 2014 and the implementation of our mobile ECMO team and the significant rise of the number of P- ARDS under ECMO in our unit. Moreover, the development of prone positioning during ECMO (18,22) and protective ventilation with controlled driving pressure (6). The main objective of this bundle was to control the ventilation pressure.

To achieve this objective, all patients were ventilated in a pressure control mode, the PEEP level was determined with the pulmonary imaging (X-ray or cross-sectional imaging), then the driving pressure was set between 14 and to be at 16 cmH_20. Finally, if the achieved tidal volume was around 4 ml/kg, a weaning procedure was started.

The period 1 was defined by the entire patient treated by ECMO before 2014 and the period 2 was defined by the entire patient treated by ECMO after 2014.

The study was approved by the Ethic Committee of our institution as an observational study and the computerized data collection was approved by the French Data Protection Authority (n°2121127V0).

Statistics:

Data analyses were performed using Stata version 13.0 (Stata Corp, College Station, TX). Categorical variables were expressed in percentage and compared using Fischer exact test. Kolgomorov analysis was performed to test the normal distribution of our continuous variables. Continuous variables were normally expressed as mean and standard deviation and compared with Welch's test. $P < 0.05$ was considered as significant.

Results:

Eighty-three patients were included during the study period (38 in period 1 and 45 for period 2). Population characteristics were similar in both groups (table 2). The use of prone positioning was significantly higher during the period 2 ($p < 0.0001$), so was the use of our mobile unit ($p < 0.0001$). Considering the pre-ECMO ventilatory setting, the PEEP (9.2 $cmH_20 \pm 0.6$ vs 11.3 $cmH_20 \pm 0.6$, p: 0.01) and the mean pressure (20.6 $cmH_20 \pm 1.2$ vs24.3 $cmH_20 \pm 1.2$, p: 0.003) were significantly higher during the period 2. There was no significant difference for the others ventilatory settings and the ECMO flow (table 3).

At day 3 of ECMO, 83 patients were still on ECMO. The pressure controlled ventilatory mode was significantly more frequent in the period 2 ($p < 0.0001$). The PEEP (8.9 $cmH_20 \pm 0.5$ vs11.9 $cmH_20 \pm 0.6$, p: 0.0002), the mean pressure (13.1 $cmH_20 \pm 0.6$ vs 15.8 $cmH_20 \pm 0.5$, p: 0.0006) and the respiratory rate (12.1/bpm ± 0.8 vs 15.4/bpm ± 0.6, p: 0.002) were significantly higher during this second period. In contrary, the driving pressure was lower in during the period 2 (15.9 $cmH_20 \pm 0.8$ vs 23.6 $cmH_20 \pm 2.5$, p: 0.009). No significant difference was identified for the others ventilatory settings and the ECMO flow (table 4).

At day 7 of ECMO, 55 patients were still under ECMO. A significantly higher level of PEEP (8.5 $cmH_20 \pm 0.7$ vs 11.9 $cmH_20 \pm 0.6$, p: 0.0002), mean pressure (12.8 $cmH_20 \pm 0.6$ vs 15.6 $cmH_20 \pm 0.6$, p: 0.001 and respiratory rate (14.0/min ± 0.1 vs 19.1/min ± 1.8, p: 0.002) was found for period 2 in comparison with period 1. Conversely, the driving pressure was lower in period 2 than in the period 1 (23.3 $cmH_20 \pm 1.9$ vs 15.1 $cmH_20 \pm 0.9$, p: 0.001). No significant difference was identified for the others ventilatory settings and the ECMO flow (table 4). Twenty-six patients remained on ECMO at day 14. PEEP (8.1 $cmH_20 \pm 0.8$ vs 13.2 $cmH_20 \pm 1.0$, p: 0.0005) and mean pressure (13.4 $cmH_20 \pm 0.8$ vs 17.1 $cmH_20 \pm 1.1$, p: 0.01) remained significantly higher in period 2 than in period 1. We still observed a lower driving pressure during the period 2 (25.7

$cmH_20 \pm 2.1$ vs 14.2 $cmH_20 \pm 0.6$, p: 0.001). No significant difference was identified for the others ventilatory settings and the ECMO flow, except for tidal volume (table 4).

Outcome criteria and adjunctive therapies were similar in both population except for the use of prone positioning which was more frequent during the period 2 than the period one (2.6 % vs 20.5 %, p: 0.01) (table 5).

We report one of the first lung protective ventilation bundle during ECMO for P-ARDS. The implantation of such a LPVB allow us the strongly decrease the ventilatory pressure during ECMO for P-ARDS. Because of this LPVB, the mechanical power of invasive mechanical ventilation during ECMO was lower. Despite theses modifications, we did not identify significant difference in survival rate between both study periods. It can be explained by the limited power of our study related to its single center characteristic. A larger application of this LPVB in several unit performing ECMO for P-ARDS might help to determine the effect of such bundle on survival rate, length of ECMO and invasive mechanical ventilation.

Discussion

We report one of the first lung protective ventilation bundle during ECMO for P-ARDS. The implantation of such a LPVB allow us the strongly decrease the ventilatory pressure during ECMO for P-ARDS. Because of this LPVB, the mechanical power of invasive mechanical ventilation during ECMO was lower. Implementing a new bundle in a unit can be a challenge due to the necessity to convince all the physician to comply with this bundle. Indeed, defining the best way to protect dysfunctional lungs still remains an unsolved question and only few publications are available in the adult population (18,23) as well as in the pediatric population (19). These studies are mainly retrospective, descriptive studies trying to identify correlation between ventilatory settings during ECMO and survival rate. Serpa Neto et al. (24) first

identified a significant correlation between driving pressure at day 3 of ECMO and a lower in-hospital survival rate. However, Schmidt *et al.* (18) failed in a larger meta-analyze to confirm these results. To our knowledge, there is no pediatric or adult study which had compared a protective ventilation setting bundle during ECMO for ARDS. We chose to sharply modify our ventilatory settings in 2014 in the light of the results of several study (6,7,25,26). In our study, we show a sharp increase of the use of prone positioning without severe adverse events. We also succeed in modifying our ventilatory pressure mainly illustrated by the strong decrease of the driving pressure throughout the ECMO run. Unfortunately, lack of power in our study prevents us to achieve a significant result. The use of apneic ventilation under ECMO seems to be the wright way to ventilate these severe patients. As an illustration of that, a recent experimental study on near apneic mechanical ventilation by Araos *et al.* (27) compared three groups of pigs under ECMO for ARDS. They defined a 1) non-protective mechanical ventilation (PEEP: 5 cm H_2O; tidal volume: 10 ml/kg; respiratory rate, 20 bpm), 2) conventional-protective (PEEP, 10 cm H_2O; Vt, 6 ml/kg; respiratory rate, 5 bpm) and 3) near-apneic (PEEP, 10 cm H_2O; driving pressure, 10 cm H_2O; respiratory rate: 20bpm). They identified a significant decrease of lung injury in the near-apneic group associated with a lower matrix metalloproteinase activity.

We noticed in our result that the respiratory rate was higher in the LPBV period despite the recommended bundle. This difference is not explained by a significant difference of age in both groups. It can be explained by the underestimated consequence of high respiratory rate during P-ARDS on power of mechanical invasive ventilation as its formula include respiratory rate. Another explanation could be that the physician in charge of patient on VA ECMO for ARDS tried to limit Harlequin syndrome by slightly increased lung ventilation without increasing ventilatory pressure.

Among all the ventilatory strategies, the use of neurally adjusted ventilatory assist could also have a significant positive impact in these patients. Assy *et al.* (28) reported the first pediatric report of Veno-Venous ECMO in six children suffering from P-ARDS. The delay for ECMO weaning was significantly shorter in the NAVA group comparing to the control group. NAVA during ECMO has already been reported in the adult ARDS under ECMO by Karagiannidis *et al.* in 2010 (29) and allowed to apply a protective mechanical ventilation with limited inspiratory pressure. These results have been confirmed by Maury *et al.* (30) in a report of 10 patients. They have shown that NAVA was associated with a lower asynchrony rate, which is probably associated with a lower ventilator induced lung injury. Nevertheless, using NAVA supposed to slightly awake the patients. Unfortunately, some severe patient cannot be awakened or suffering from a too severe diaphragmatic dysfunction and using NAVA may be inefficient (31). Finally, the use of prone positioning during ECMO for P-ARDS increase in our study. This procedure is now widely spread for the treatment of severe ARDS (7,32) but its use did not result in any recommendation during ECMO for ARDS. Therefore, several study on its safety (33) and usefulness are now available and show an improvement of survival rate in the ECMO associated with prone positioning group (34–36).

Conclusion:

Ventilatory settings in patients under ECMO for P-ARDS are a challenging question and the appliance of apneic protective ventilation could be the best way to heal the dysfunctional lungs. Implementation of a bundle is probably an efficient way to achieve this objective. However, largest studies on this topic are urgently needed to obtain significant more powerful results.

Dr Rambaud Jerome have given a substantial contribution to the conception wrote and designed the study, collected the data, wrote and reviewed the manuscript

Dr Jegard Julien, Dr Levy Yael, Dr Guellec Isabelle and Dr Rambaud Jerome have given a substantial contribution to acquisition and analysis of the data.

All authors critically reviewed the manuscript.

All authors have participated to the drafting of the manuscript. All authors read and approved the final version of the manuscript.

The authors have no conflicts of interest to declare

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Pressure control ventilation
FiO_2: decrease under 60% during the first 24h
Positive end expiratory pressure between 8 and 12 cm H_20
Inspiratory pressure: 12 to 16 cm H_20 above the PEEP
Respiratory rate between 10 and 20 breath per minute
Observed Tidal volume lower than 5 ml/kg

Table 1: ventilatory bundle during ECMO for pediatrics Acute Respiratory Distress Syndrome

FiO2: inspired fraction of oxygen, PEEP: positive end expiratory pressure

Demographic datas	**Period 1 (N= 38)**	**Period 2 (N= 45)**	
Age (days)	1012 ± 225	846 ± 171	NS
Weight (kg)	14 ± 3	11 ± 2	NS
Male (%)	58.9 (N : 23)	54.4 (N : 25)	NS
Oxygenation index	35.6 ± 2.8	43.4 ± 3.7	NS
PaO_2/FiO_2 ratio	63.3 ± 4.2	62.3 ± 5.0	NS
OSI	26.3 ± 2.3	29.9 ± 3.8	NS
PELOD (%)	15.2 ± 3.7	18.8 ± 3.7	NS
PIM II (%)	19.6 ± 4.2	14.2 ± 2.5	NS
< 37 GA (%)	12.8 (N : 5)	17.4 (N : 8)	NS
Home oxygene dependant (%)	0 (N : 0)	6.5 (N : 3)	NS
Immunocompromised (%)	15.4 (N : 6)	21.2 (N : 10)	NS
Influenza (%)	12.8 (N : 5)	10.9 (N : 5)	NS
Viral pneumonia (%)	47.7 (N :21)	52.3 (N : 23)	NS
Pulmonary hemorrhage (%)	7.7 (N : 3)	4.4 (N : 2)	NS
Bacterial pneumonia (%)	32.4 (N : 12)	42.5 (N : 20)	NS
Fungique pneumonia (%)	2.6 (N : 1)	2.2 (N :1)	NS
Acute asthma (%)	5.1 (N : 2)	6.5 (N : 3)	NS

Table 2: Demographics characteristics

FiO2: inspired fraction of oxygene, GA: gestational age, OSI: oxygenation saturation index, PaO2: partial pressure of arterial oxygen, PaCO2: partial pressure of arterial carbon dioxide

Pre-ecmo characteristics	Period 1 (N= 38)	Period 2 (N= 45)	P value
Intervalle PICU ECMO (days)	5.3 ± 0.8	4.1 ± 0.5	NS
Intervalle intubation ECMO (days)	3.9 ± 0.6	4.3 ± 0.7	NS
Mobile unit (%)	0 (N : 0)	43.5 (N :20)	P < 0.0001
Prone positioning (%)	10.3 (N : 4)	65.2 (30)	P < 0.0001
Neuromuscular blockers (%)	89.7 (N :35)	97.8 (N :45)	NS
High frequency oscillation (%)	38.5 (N :15)	30.4 (N :14)	NS
Nitours oxide	53.8 (N :21)	47.8 (N :22)	NS
Pre ECMO volumetric ventilation	66.7 (N : 26)	65.2 (N : 30)	NS
Pre-ecmo tidal volume (ml/kg)	6.5 ± 0.2	7.1 ± 0.3	NS
Pre ECMO frequency (/bpm)	39 ± 2	44 ± 2	NS
Pre-ECMO mean pressure (cmHz0)	20.6 ± 1.2	24.3 ± 1.2	p : 0.003
Pre-ECMO plateau pressure (cmHz0)	38.7 ± 2.8 (N : 10)	35.9 ± 1.9 (N : 28)	NS
Pre-ECMO PEEP (cmH20)	9.2 ± 0.6	11.3 ± 0.6	p : 0.01
Pre-ECMO driving (cmHz0)	27.8 ± 2.7 (N : 10)	24.8 ± 1.9 (N : 28)	NS
Pre-ECMO PaO2 (mmHg)	64.5 ± 4.5	66.5 ± 4 .1	NS
Pre-ECMO PaCO2 (mmHg)	65.2 ± 4.5	61.2 ± 4.7	NS
Pre-ECMO pH	7.3 ± 0.03	7.2 ± 0.02	NS
Pre-ECMO lactate (mmol/I)	2.1 ± 0.3	2.6 ± 0.5	NS
Pre-ECMO pulmonary air leaks (%)	17.9 (N:7)	4.4 (N:2)	NS
Pre-ECMO renal replacement therapy (%)	0 (N: 0)	4.4 (N:2)	NS

Table 3: characteristics before ECMO implantation

ECMO extracorporeal membrane oxygenation, FiO^2: inspired fraction of oxygen, GA: gestational age, OSI: oxygenation and saturation index, PaO^2: Partial pressure of arterial oxygen, $PaCO^2$: Partial pressure of arterial carbon dioxide, PEEP: positive end expiratory pressure, PICU: pediatric intensive care unit

Ventilatory settings	**Period 1** (N= 38)	**Period 2** (N= 45)	P value
Day 3 volumetric ventilation (%)	48.7 (N:19)	6.4 (N:3)	p < 0.0001
Day 3 ECMO flow (ml/kg/min)	91.6 ± 8.1	92.1 ± 4.1	NS
Day 3 tidal volume (ml/kg)	4.5 ± 0.2	4.1 ±0.4	NS
Day 3 PEEP (cmH_20)	8.9 ± 0.5	11.9 ± 0.6	0.0002
Day 3 respiratory rate (/bpm)	12.1 ± 0.8	15.4 ± 0.6	p : 0.002
Day 3 mean pressure (cmH_20)	13.1 ± 0.6	15.8 ± 0.5	0.0006
Day 3 driving pressure (cmH_20)	23.6 ± 2.5	15 ± 0.8	p: 0.009
Day 3 renal replacement therapy (%)	16.7 (N :4)	4.4 (N :4)	NS
	Period 1 (N= 27)	**Period** 2 (N= 28)	
Day 7 volumetric ventilation	40.7 (N :11)	21.4 (N :6)	NS
Day 7 ECMO flow (ml/kg/min)	87.9 ± 9.8	98.1 ± 5.8	NS
Day 7 tidal volume (ml/kg)	4.2 ± 0.3	41.1 ± 0.5	NS
Day 7 PEEP (cmH_20)	8.5 ± 0.7	11.9 ± 0.6	p : 0.0002
Day 7 respiratory rate (/bpm)	14 ± 0.1	19.1 ± 1.8	p : 0.002
Day 7 mean pressure (cmH_20)	12.8 ± 0.6	15.6 ± 0.6	p : 0.001
Day 7 driving pressure (cmH_20)	23.3 ± 1.9	15.1 ± 0.9	p : 0.001
Day 7 renal replacement therapy (%)	3.9 (N :1)	10.7 (N :3)	p : 0.001
	Period 1 **(N= 11)**	**Period** 2 (N= 13)	
Day 14 volumetric ventilation	36.4 (N :4)	8.3 (N :1)	NS
Day 14 ECMO flow (ml/kg/min)	102.6 ± 18.5	110.9 ± 7.6	NS
Day 14 tidal volume (ml/kg)	5.5 ± 0.4	2.5 ± 0.5	p < 0.0001
Day 14 PEEP (cmHz0)	8.1 ± 0.8	13.2 ± 1.0	p : 0.0005
Day 14 respiratory rate (/bpm)	19.4 ± 4.1	15.7 ± 1.4	NS

Day 14 mean pressure (cmH_20)	13.4 ± 0.8	17.1 ± 1.1	p : 0.01
Day 14 driving pressure (cmH_20)	25.7 ± 2.0	14.2 ± 0.6	p : 0.001
Day 14 renal replacement therapy (%)	9.1 (N :1)	15.4 (N :2)	NS

Table 4: ventilatory settings at day 3, 7 and 14 of ECMO

ECMO: extracorporeal membrane oxygenation, PEEP: positive end-expiratory pressure

Outcomes and adjunctive therapies	Period 1 (N= 38)	Period 2 (N= 45)	P value
Prone positioning during ECMO (%)	2.6 (N :1)	20.5 (N :9)	p : 0.01
Use of steroids during ECMO (%)	46.2 (N :18)	45.7 (N :21)	NS
Lenght of ECMO (days)	12.2 ± 1.8	15.9 ± 3.4	NS
Lenght of invasive mechanical ventilation (days)	25.9 ± 3.3	28.1 ± 3.3	NS
Length of renal replacement therapy (days)	2.7 ± 1.3	4.0 ± 2.5	NS
Lenght of PICU stay (days)	31.6 ± 3.7	33.5 ± 4.0	NS
Lenght of hospital stay (days)	40.1 ± 5.2	46.7 ± 5.4	NS
Survival rate	53.8 (N :21)	60.9 (N :28)	NS

Table 5: Outcomes and adjunctive therapies criteria

ECMO: extracorporeal membrane oxygenation, PICU: pediatric intensive care unit