Retrospective Analysis of Arterial Carbon Dioxide Level and Arterial pH Level at the Time of Initiation of Respiratory ECMO and Outcome

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Abstract

Introduction Respiratory extracorporeal membrane oxygenation (ECMO) is well established and its popularity has increased during coronavirus disease 2019 (COVID-19) time. The efficacy of ECMO has been proved in refractory respiratory failure with varied etiology. More than 85,000 respiratory ECMO cases (neonatal, pediatric, adult) registered as per Extracorporeal Life support Organization (ELSO) statistics April 2022 report, with survived to discharge or transfer ranging from 58 to 73%. Early initiation of ECMO is usually associated with shorter ECMO run and better outcome. Many patient factors have been associated with mortality while on ECMO. Pre-ECMO patient pH and arterial partial pressure of carbon dioxide (paCO2) have been associated with poor outcome. We designed a retrospective study from a single tertiary care center and analyzed our data of all respiratory ECMO (neonatal, pediatric, and adult) to understand the effect of pre ECMO, paCO2, and arterial pH to ECMO outcome.

Methods It is a retrospective analysis of data collected of patients with acute respiratory failure managed on ECMO from January 2010 to December 2021. Pre-ECMO (1–6 hours before initiation), paCO2, and arterial pH level were noted and analyzed with primary and secondary outcome. Primary outcome goal was survivor and discharged home versus nonsurvivor, while secondary goal was the number of ECMO days and incidence of neurological complications. The statistical analysis was done for primary outcome and incidences of neurological complications and *p*-value obtained by using chi-squared method. Meta-analysis was done by classifying the respiratory ECMO cases in three major category—COVID-19, H1N1 non-COVID-19, and H1N1 respiratory failure.

Results The total 256 patients of respiratory failure were treated with ECMO during specified period by Riddhi Vinayak Multispecialty Hospital ECMO team. Data analysis of 251 patients (5 patients were transferred for lung transplant, hence been not included

Keywords
- COVID-19
- pH and outcome
- H1N1
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- respiratory ECMO

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in study) done. Patients were divided on the basis of pH level less than 7.2 and more than 7.2 and analyzed for primary and secondary outcome. Similarly, patients were divided on the basis of paCO2 level of less than 45 and more than 45.
Patient with pre-ECMO pH level more than 7.2 has statistically better survived extracorporeal life support (ECLS) (*p*-value: 0.008) and survival to discharge home (*p*-value: 0.038) chances. Pre-ECMO paCO2 level of less than 45 also showed better survival chance of survived ECLS (46.67 vs. 36.02) and survived to discharge home (42.22 vs. 31.06) but not statistically significant (*p*-value: 0.15 and 0.18, respectively). There was no significant difference in average number of ECMO days in patient survived to discharge home with paCO2 less than 45 and more than 45 (15.7 vs. 11.1 days), and also in pH more than 7.2 and pH less than 7.2 (15.8 vs. 11.6). The incidence of neurological complications was also found lower in patient with pH more than 7.2 (7.5 vs. 17.3%, *p*-value: 0.034) and in paCO2 level of less than 45 (4.4 vs. 12.65, *p*-value: 0.15).
Conclusion Pre-ECMO arterial pH of more than 7.2 (statistically significant) and paCO2 of less than 45 (statistically not significant) have definitely better survival chances and have lesser incidences of neurological complications. There was no significance difference in the number of ECMO days in either group. Authors recommends early initiation of ECMO for mortality and morbidity benefits.

Introduction

Utility of extracorporeal technologies in critical care unit is expanding, especially the continuous renal replacement therapy (CRRT) and respiratory extracorporeal membrane oxygenation (ECMO). Respiratory ECMO was initially limited to neonatal and pediatric population but after Cesar trial (2006) and pandemic of H1N1(2009) ECMO in adult cases also got the boost and in coronavirus disease 2019 (COVID-19) era it got well popularized. This can be well understood by growing number of total respiratory ECMO cases in Extracorporeal Life Support Organization (ELSO) registry. In April 2022 statistics has more than 88,000 respiratory ECMO cases (~ 51% of total cases registered) with survival to discharge around 58 to 73%.[1] Many factors affect the outcome of ECMO, one among them is pre-ECMO pH and arterial partial pressure of carbon dioxide (paCO2) level. A significant proportion of patients has hypercapnia before ECMO initiation. EOLIA (Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome) trial also had 47% of patients with a paCO2 of more than 55 mm Hg.[2] Schmidt et al in 2014 analyzed ELSO Registry data and found a higher pre-ECMO paCO2 was associated with increased mortality in patients receiving ECMO.[3] Hypercapnia and respiratory acidosis are likely a marker of underlying disease severity. Our center planned to analyze our data to find out correlation of pre-ECMO paCO2 and pH level with outcome.

Method

We designed a retrospective observational study of all respiratory ECMO (neonatal, pediatric, and adult) patient managed by Riddhi Vinayak Multispecialty Hospital team from January 1, 2010 to December 31, 2021. We extracted data on all patients who received ECMO primarily for respiratory failure from our institutional ECMO database. All ECMO modalities were included: venovenous, venoarterial, or hybrid. We created two groups of survivor versus nonsurvivor which were compared by bivariate analysis with regard to demographics and clinical and ECMO course characteristics. Differences between the two groups were analyzed and *p*-value obtained by using chi-squared two variant calculators. *p*-Value less than 0.05 is considered significance. Data was analyzed for primary outcome goal of survival to discharge home and secondary outcome goal of number of ECMO days and the incidence of neurological complications. Data analysis was done with pre-ECMO paCO2 level more than 45 and less than 45 with primary and secondary outcome goal. Similarly, data was analyzed for pre-ECMO pH level less than 7.20 or more than 7.20.

Results and Analysis

Total patients who received respiratory ECMO in our institute during specified period were 256. We have subclassified (on the basis of diagnosis) the data in three broad categories of COVID-19, H1N1, and other causes of respiratory ECMO (non-COVID-19/ H1N1). As our primary goal was survival to discharge home, we have excluded five patients who have been shifted for transplant facilities. So, overall patients data analyzed was of 251. Results from our analyzed data are as follows.

- Out of 256 respiratory ECMO, 23% patients were COVID-19, 36% H1N1, and 41% non-COVID-19/ H1N1. Overall survival in respiratory ECMO was around 38% with

Table 1 Total Respiratory ECMO from January 2010 to December 2021

	Survival	Nonsurvival	Total	Percentage of survival
COVID-19	14	44	58	24.14
H1N1	38	55	93	40.86
Non-H1N1/ COVID-19	45	60	105	42.86
Total	97	159	256	37.89
Non-H1N1	59	104	163	36.19
Non-COVID-19	83	115	198	41.92

Abbreviations: COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation.

Table 2 Pre-ECMO paCO2 and outcome in respiratory ECMO

PaCO2 less than 45 at initiation and outcome in respiratory ECMO—survived to discharge						
	Survived	Mortality	Total	Percentage of survived	Total ECMO days	Avg ECMO days
COVID-19	2	6	8	25	30	15
H1N1	5	10	15	33.33	75	15
Non-H1N1/ COVID-19	12	10	22	54.54	106	8.83
Total	19	26	45	42.22	211	11.10
PaCO2 more than 45 at initiation and outcome in respiratory ECMO—survived to discharge						
	Survived	Mortality	Total	Percentage of survived	Total ECMO days	Avg ECMO days
COVID-19	5	40	45	11.11	216	43.2
H1N1	29	49	78	37.18	510	17.58
Non-H1N1/ COVID-19	30	53	83	36.14	281	9.36
Total	64	142	206	31.06	1007	15.73

Abbreviations: COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; paCO2, partial pressure of carbon dioxide.

maximum in non-COVID-19/H1N1 respiratory failure approximately 43% and least in COVID-19 approximately 24% (see ►**Table 1**).

- Most of the patient had type II respiratory failure (paCO2 >45 in 82.5%) and mixed or predominant respiratory acidosis (pH <7.4 in $\sim$ 84%) at the time of initiation of ECMO.
- Survival to discharge chances were better in group with paCO2 less than 45 (42.2 vs. 31.06); however, on statistical analysis it was not significant (p-value: 0.15) (see ►**Tables 2** and **3**). There was not much difference in average paCO2 of survival to discharge (63.3) and in nonsurvivor (66.8) (►**Fig. 1**).
- Survival to discharge chances were better in group with pre-ECMO pH less than 7.2 (42.2 vs. 31.06) and were also statistically significant (p-value: 0.038) (►**Table 4**).
- In meta-analysis, there was no difference in outcome of H1N1 patient with paCO2 level. However, in COVID-19 patient (25 vs. 11.11%) and non-COVID-19/H1N1 (54.54 vs. 36.14) had better survival with paCO2 less than 45 mmHg (see ►**Table 2**).
- There was no significant difference in number of ECMO days, in patient with paCO2 less than 45 or more than 45 (11.1 vs. 15.7 days) and similarly with pH of less than 7.2 or more than 7.2, also there was no significance difference (11.6 vs. 15.8 days)

Table 3 Pre-ECMO paCO2 and outcome in respiratory ECMO with p-value

PaCO2 Level	Survival	Nonsurvival	p-Value
COVID-19			
<45	2	6	0.28
>45	5	40	
Total	7	46	
H1N1			
<45	5	10	0.77
>45	29	49	
Total	34	59	
Non-COVID-19/ H1N1			
<45	12	10	0.12
>45	30	53	
Total	42	63	
Total respiratory failure			
<45	19	26	0.15
>45	64	142	
Total			

Abbreviations: COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; paCO2, partial pressure of carbon dioxide.

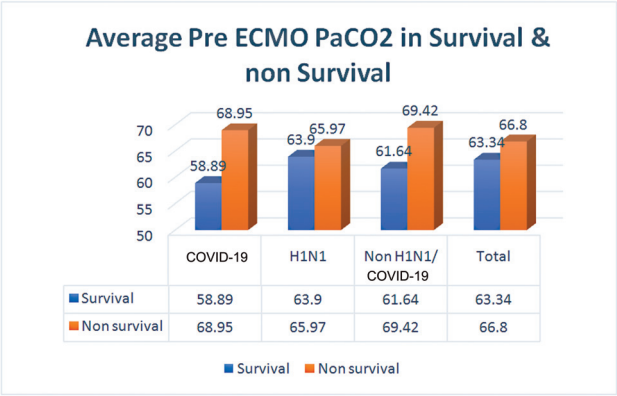

Fig. 1 Average pre-extracorporeal membrane oxygenation partial pressure of carbon dioxide in survival and nonsurvival. COVID-19, coronavirus disease 2019.

- Total adverse neurologic events diagnosed by neuroimaging and clinical findings occurred in 28 of 251 (11.15%) patients, predominantly diagnosed was intracranial haemorrhage in 14 of 251 i.e. 5.57% of patients and PCO2 too remained high as shown in ►**Figure 2** (►**Table 5**). However, the true prevalence of neurologic injuries in survivors and nonsurvivors was unknown secondary to the elective nature of neuroimaging.
- Incidence of neurological complications was much low not only in pre-ECMO paCO2 of less than 45 (4.4 vs. 12.6) (►**Table 5**) but also in pre-ECMO pH less than 7.2 (17.39 vs. 7.55, *p*-value 0.034) (►**Table 6**).

Conclusion

In our analysis, we found most (> 80%) of the patients who required respiratory ECMO were in type II respiratory failure and in respiratory or mixed acidosis. These numbers are significantly higher as compared to the numbers in EOLIA trial (47% only). Also, both higher $paCO_2$ level and lower pH at the time of initiation of ECMO are related to higher mortality and risk of neurological complications. However, only pre-ECMO lower pH was found statistically significant for both mortality and neurological complications. So, early initiation of ECMO with pre-ECMO paCO2 less than 45 and pH more than 7.2 has better survival chances.

Discussion

Many of the times patients who require respiratory ECMO are hypercapnic and/or in acidosis. This is because of our routine ventilatory management practice of permissive hypercapnia. Respiratory acidosis and pre-ECMO elevations of paCO2 have been associated with poor outcomes from ECMO.[4,5] In older children, Mehta et al found that higher pH (pH > 7.2) before ECMO initiation was associated with increased survival.[4] Also, pre-ECMO elevated paCO2 (>50 mmHg) is associated with ICH in neonates rescued with ECMO.[5,6] In other studies of pediatric ECMO, duration of mechanical ventilation and serum pH less than 7.29 before ECMO initiation has been associated with increased mortality.[7]

There is no clear mechanism for elevated paCO2 to "actively" contribute to increased mortality except through the physiologic effect of paCO2 on the brain. Rapid corrections of patient's paCO2 and pH could adversely affect cerebral blood

Table 5 Incidence of neurological complications and $paCO_2$ level

	< 45	> 45
IC bleeding	1	13
Brain dead	1	13
Total	2	26
Total cases	45	206
Percentage of complication	4.44	12.62

Abbreviations: IC, intracranial; paCO2, partial pressure of carbon dioxide.

Table 6 Incidence of neurological complications and pH level

	< 7.2	> 7.2	Total	*p*-Value
Total complications	16	12	28	0.034
Total cases	92	159	251	
Percentage of complications	17.39	7.55	11.15	

Table 4 pH level and outcome in respiratory ECMO

pH initiation	Total	Survived	Mortality	Percentage of survival	LOS	Avg ECMO days	*p*-Value
Survived to discharge							**0.038**
< 7.2	92	23	69	25	268	11.65	
> 7.2	159	60	99	37.73	950	15.83	
	251	83	168	33.07			
Survived ECLS							**0.008**
< 7.2	92	25	67	27.17			
> 7.2	164	72	92	43.90			
	256	97	159	37.89			

Abbreviations: ECMO, extracorporeal membrane oxygenation; ECLS, extracorporeal life support.

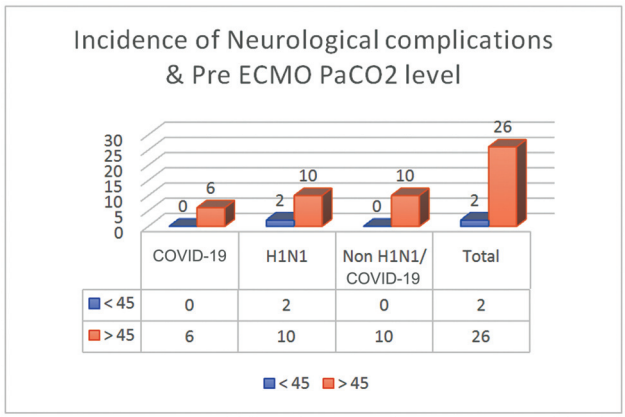

Fig. 2 Neurological complications and partial pressure of carbon dioxide level. COVID-19, coronavirus disease 2019.

flow and perhaps contribute to increased neurologic injury and poor outcome.[8–10] Careful attention to the rate of correction of paCO2 has been advocated in these patients.

Summary

Our study has the limitations inherent to the retrospective design and single-center experience. But many other retrospective studies also have similar experience of poor outcome associated with pre-ECMO hypercapnia and acidosis (respiratory or mixed) in respiratory ECMO. Also, rapid corrections post-initiation of ECMO leads to neurological complications like IC bleed. Authors strongly recommend early initiation of ECMO and slow corrections $paCO_2$ post-initiation of ECMO for a better outcome.

Conflict of Interest
None declared.

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