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Pulmonary Congestion (White Lungs) on VA ECMO

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Abstract

Background

Veno-arterial extracorporeal membrane oxygenation therapy (VA ECMO) is used for short-term circulatory support in the setting of cardiogenic shock or cardiac arrest. While VA-ECMO improves hemodynamics and gas exchange, it may result in left ventricular distention and pulmonary congestion.

Methods

The records of all patients supported with VA ECMO for at least three consecutive days at our institution from 2012-2014 were retrospectively analyzed. All chest radiographs taken during VA ECMO support were graded on a scale of 1 to 4. A score of 1 was used when no pulmonary congestion was present. A score of 2 was used for congestion occupying less than half of both lungs. A score of 3 was used for diffuse congestion occupying over half of both lung fields. A score of 4 was used when complete opacification of both lungs was present. Grades 3 and 4 were considered “white lungs”. The presence of white lungs was examined as a categorical variable. The grade of congestion was examined as a continuous variable. Ordinal logistic regression was used for the analysis.

Results

The sample size analyzed included 46 events of VA ECMO support in 44 individual patients. In 34 (73.9%) patients the lungs became opacified and reached a score of 3 or 4 (the white lungs group), while in 12 (%) patients there were no white lungs.

Overall, the percentage of patients that survived to weaning off VA ECMO was 60.9%. The percentage of patients that survived to hospital discharge was

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37.0%. In patients who did not have white lungs the percentages of survival to weaning off VA ECMO and survival to hospital discharge were 91.7% and 66.7%, respectively. In those with white lungs, the percentages of survival to weaning off VA ECMO and survival to hospital discharge were 50.0% and 26.5%, respectively (p=0.019 for discharged alive).

The duration of VA ECMO support, ECMO flow, daily fluid balance, sum net fluid balance for the length of stay, and use of hemodialysis predicted a higher degree of pulmonary congestion.

Conclusion

Severe pulmonary congestion, or white lungs, is common in patients on VA ECMO and is associated with very poor prognosis. Longer duration of support, greater positive fluid balance, higher ECMO flow, and use of hemodialysis are linked to development of white lungs.

Keywords

Heart failure; cardiogenic shock, ECMO; pulmonary edema

Abbreviations

Alb	Albumin
AMI	Acute myocardial infarction
CI	Confidence intervals
CPR	Cardiopulmonary resuscitation
CXR	Chest radiograph
HD	Hemodialysis
HF	Heart failure
LOS	Length of stay
PE	Pulmonary embolism
RVF	Right ventricular failure
VA ECMO	Veno-arterial extracorporeal membrane oxygenation therapy

Introduction

Veno-arterial extracorporeal membrane oxygenation therapy (VA ECMO) is used for short-term circulatory support in the setting of cardiogenic shock or cardiac arrest. While VA ECMO improves hemodynamics and gas exchange, it may result in left ventricular distention and pulmonary congestion. Creating a retrograde aortic flow, ECMO can increase left ventricular end diastolic pressure and therefore precipitate left ventricular failure, manifesting as pulmonary congestion/edema.

The phenomenon analyzed in this paper is referred to as “ECMO lungs” or “left ventricular distension”. In this manuscript it is referred to as “white lungs” to reflect the extreme opacification of both lung fields to the degree that would be incompatible with life if gas exchange was not provided by the oxygenator. The prevalence of this condition, effects on survival, and factors associated with its development are largely unknown in the adult population treated for cardiogenic shock.

Methods

The records of all patients supported with VA ECMO for at least 3 consecutive days at The University of Kentucky Medical Center from 2012- 2014 were retrospectively analyzed. Each patient was supported by VA ECMO and had a daily chest radiograph (CXR). Data measuring central venous pressure, systolic, diastolic, and mean arterial pressure, daily fluid balance, and the net fluid balance while supported with VA ECMO were collected.

The daily CXR for each patient supported with VA ECMO was reviewed. All patients with gross pre-existing lung pathology such as diffuse fibrosis or conditions involving only one lung such as pneumothorax, hemithorax, bronchial occlusion, etc. were excluded from this analysis. Based on the degree of lung opacification, all CXRs were graded on a scale of 1 to 4. A score of 1 was used when no pulmonary congestion was present. A score of 2 was used for congestion occupying less than half of both lungs. A score of 3 was used for diffuse congestion occupying over half of both lung fields. A score of 4 was used when complete opacification of both lungs was present. (Figures 1-4). The scoring was done initially by two cardiologists and then independently by the radiologist who was blinded to clinical information.

If an individual patient had more than half of the lung fields opacified (score of 3 or 4) at any time while being supported by VA ECMO they were included into the white lungs group.

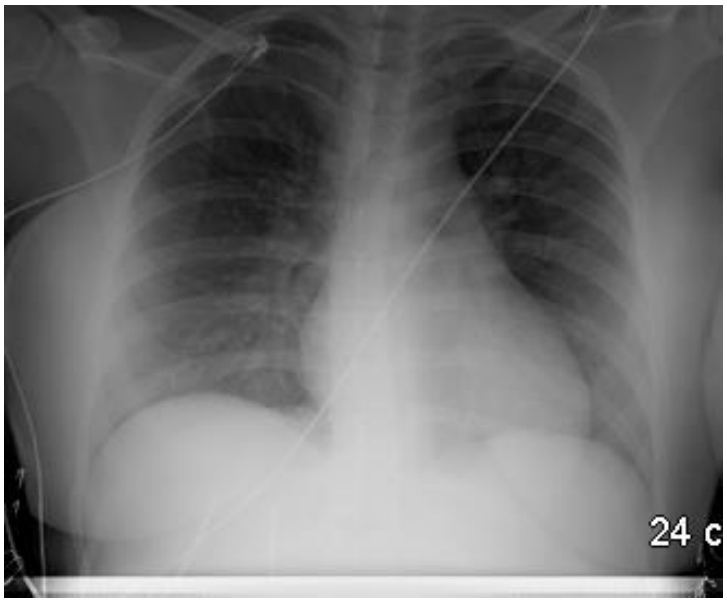

Figure 1. Grade 1

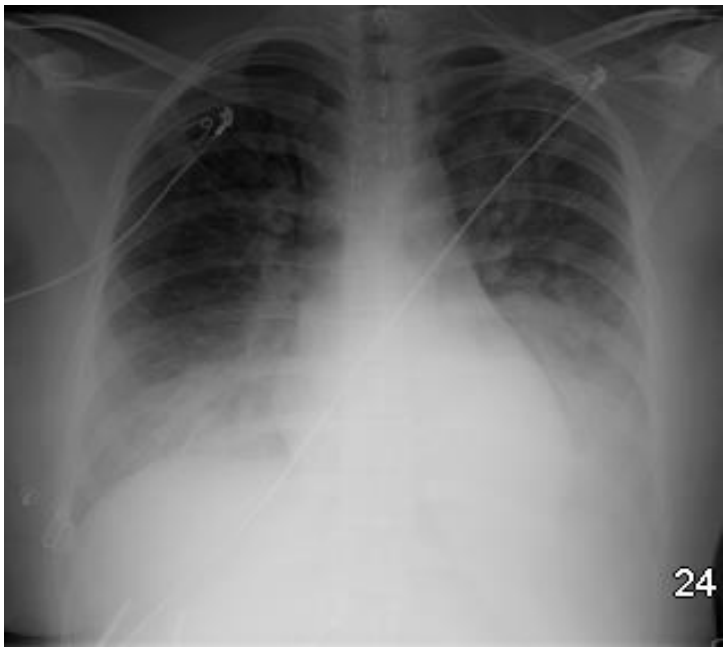

Figure 2. Grade 2

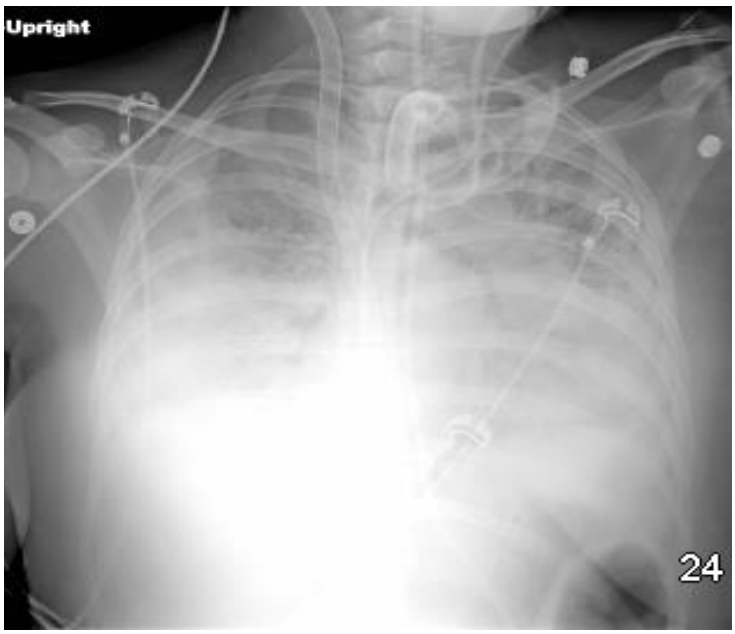

Figure 3. Grade 3

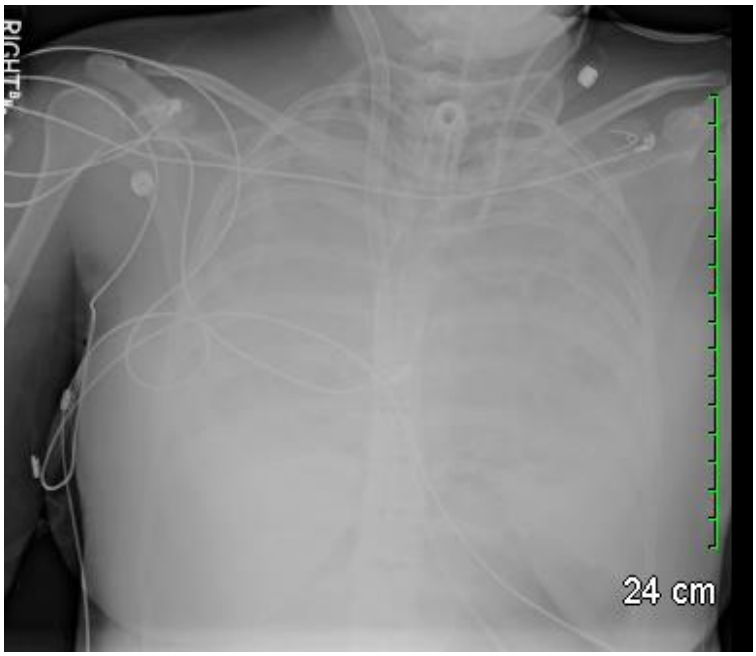

Figure 4. Grade 4

All patients were grouped into the following categories based on their indication for use of VA ECMO support: cardiac arrest, acute myocardial infarction, heart failure (HF), right ventricular failure not secondary to acute pulmonary embolism, acute pulmonary embolism, and postcardiotomy syndrome. All cases where VA ECMO support was initiated during cardiopulmonary resuscitation (CPR) or immediately following restoration of spontaneous circulation following CPR were classified as cardiac arrest regardless of the underlying etiology of cardiac arrest.

Presence of white lungs was examined as a binary variable, and grade of congestion as an ordinal variable. Wilcoxon rank sum test and Fisher's exact test were used to compare groups of persons on numeric and binary variables respectively; Spearman's correlation was used to assess association between two numeric variables (or one numeric and one ordinal variable). Ordinal logistic models were used to relate several factors to maximal and day-specific measurements of congestion; to clarify the terminology by an example, a person with three consecutive day-specific measurements of 2, 2, and 3 would have a maximal measurement of 3 (and an average measurement of 2.33). Version 9.3 of SAS was used to analyze data, and statistical significance was defined by a p-value < 0.05.

Results

106 events of VA ECMO support occurred during the time of this analysis. Events were excluded from this analysis if the patient was supported with VA ECMO for less than three days (46 events). Also, 14 events where the patients had focal pulmonary abnormalities on pre-ECMO CXR (hemithorax, main bronchus occlusion, idiopathic pulmonary fibrosis, etc.) were excluded. The final dataset consisted of 46 events in 44 patients. The mean age was 51.6 ±16.5 years, and 31.8% of the patients analyzed were females. Central cannulation was used in 14 cases (30.4%). Cannulae were placed in femoral vein/femoral artery in all other cases.

Other pertinent characteristics were left ventricular ejection fraction (mean 26.1±17.6%) and pulmonary capillary wedge pressure (23.9±11.5 mmHg)_

In 34 (73.9%) patients, lungs became opacified and reached score of 3 or 4 (the white lungs group) while in 12(%) patients there were no white lungs.

Overall, the percentage of patients that survived to weaning off VA ECMO was 60.9%. The percentage of patients that survived to hospital discharge was 37.0%. In patients who did not have white lungs the percentages of survival to weaning off VA ECMO and survival to hospital discharge were 91.7% and 66.7%, respectively. In those with white lungs, the percentages of survival to weaning off VA ECMO and survival to hospital discharge were 50.0% and 26.5%, respectively (p=0.019 for discharged alive).

Referring to the categories created to indicate the etiology of cardiogenic shock, patients developed white lungs in each group, and this phenomenon was

associated with poor survival (Table 1). Although the sample size is limited, there was a trend for patients supported with VA ECMO due to cardiac arrest, postcardiotomy syndrome, and HF to develop white lungs more frequently than in other conditions. Duration of support was longer for patients with white lungs.

Table 1. Survival to weaning off ECMO and to discharge depending on the presence of white lungs.

	N	%	Survived on ECMO	%	Survi-ved to dis-charge	%	LOS	Duration of support	HD	%	Alb	%
Total	46		28	60.9	17	37.0	28 [12-60]	6 [4-11]	17	37.8	18	40.0
White lungs	34	73.9	17	50.0	9	26.5	23.5 [10-55]	6.5 [4-12]	16	47.1	16	48.5
No white lungs	12	26.1	11	91.7*	8	66.7*	33.5 [22-69.5]	4 [3-6]*	1	9.1*	2	16.7
Cardiac arrest	14		7	50.0	4	28.6	26 [10-74]	6 [4-7]	5	38.5	6	42.9
White lungs	11	78.6	4	36.4	1	9.1	18 [5-55]	7 [4-9]	4	36.4	6	54.5
No white lungs	3	21.4	3	100	3	100*	92 [28-121]	4 [3-6]	1	50.0	0	0.0
Acute myocardial infarction	6		5	83.3	2	33.3	24 [11-29]	5 [4-6]	2	33.3	2	33.3
White lungs	3	50.0	2	66.7	1	33.3	20 [3-29]	4 [3-6]	2	66.7	1	33.3
No white lungs	3	50.0	3	100	1	33.3	28 [11-64]	6 [4-8]	0	0.0	1	33.3
Heart Failure	16		11	68.8	8	50.0	23.5 [16-86.5]	5.5 [4-12]	5	31.3	5	33.3
White lungs	13	81.3	8	61.5	6	46.2	23 [16-98]	11 [5-12]	5	38.5	5	41.7
No white lungs	3	18.7	3	100	2	66.7	35 [16-75]	4 [3-5]	0	0.0	0	0.0
Pulmonary embolism	1		1	100	1	100	32 [na]	3 [na]	0	0.0	0	0.0
White lungs	0	0.0	0	na	0	na	na	na	0	na	0	na
No white lungs	1	100	1	100	1	100	32 [na]	3 [na]	0	0.0	0	0.0

Right Ventricular Failure	3		3	100	2	66.7	57 [45-68]	16 [6-32]	2	66.7	2	66.7
White lungs	2	66.7	2	100	1	50.0	56.5 [45-68]	24 [16-32]	1	50.0	1	50.0
No white lungs	1	33.3	1	100	1	100	57 [na]	6 [na]	1	100	1	100
Postcardio-tomy syndrome	5		1	20.0	0	0.0	14 [12-51]	4 [3-5]	3	60.0	3	60.0
White lungs	4	80.0	1	25.0	0	0.0	32.5 [10-53]	4.5 [3.5-9.5]	3	75.0	2	50.0
No white lungs	1	20.0	0	0.0	0	0.0	12 [na]	3 [na]	0	0.0	1	100

* indicates P < 0.05 versus comparable subgroup with white lungs using Wilcoxon rank sum test (LOS and duration of support; Median and interquartile range also shown) and Fisher's exact test (Survived on ECMO, Survived to discharge, HD, and Alb). Note, one person had a missing value on HD, and one person had a missing value on Alb; percentages are calculated accordingly.

Duration of ECMO support, ECMO flow, daily fluid balance, sum net fluid balance for the length of stay, and being on hemodialysis predicted higher degree of pulmonary congestion (Table 2.) Systolic, diastolic, pulse, or mean systemic pressure, or mean central venous pressure were not predictors of white lungs or higher CXR score. Left ventricular ejection fraction by echo and pulmonary capillary wedge pressure by Swan-Ganz catheter was not associated with the severity of pulmonary congestion.

Mechanical ventilatory support was used (synchronized intermitted mandatory ventilation) in 36 (78.3%) cases. The mean tidal volume was 483±83.7 mL, mean peep pressure was 6.1±1.2 mmHg, mean respiratory rate was 13.5± 3.1 per minute, and mean FiO2 was 48.5±7%. There was no difference between the white lung group and no white lung group by any of the parameters.

Systolic, diastolic, pulse, and mean arterial pressure, as well as central venous pressure were not significant predictors of maximal CXR score; among several factors examined, only albumin use was (estimated unadjusted odds ratio 3.382, 95% CI 1.027 to 11.131, p-value = 0.0450).

In 34 patients with white lungs, 14 had severe pulmonary opacification prior to the initiation of VA ECMO. Only 3 of them improved on support. In 20 patients, white lungs developed while on VA ECMO support. In this group, mean time to

the development of white lungs was 5.0+/-3.8 days. 10 of them improved while on VA ECMO support.

Table 2. Factors predicting white lungs on VA ECMO

Predictor	Estimate of odds ratio	Lower limit of 95% CI	Upper limit of 95% CI	p-value
Time (days on ECMO)	1.236	1.185	1.289	<.0001
Net daily balance	1.107	1.028	1.193	0.0077
Sum net balance	1.130	1.093	1.167	<.0001
ECMO Flow	1.845	1.316	2.587	0.0004
Ventilator	0.704	0.302	1.643	0.4175
Hemodialysis	2.875	1.125	7.350	0.0282
Mean arterial pressure	0.983	0.967	1.000	0.0524

Results are based on ordinal logistic mixed models. Each odds ratio estimate is not adjusted for the other variables considered. By virtue of the ordinal logistic modeling, the odds ratios pertain simultaneously to dichotomizations of “4 vs. 3 or lower”, “3 or higher vs. 2 or lower”, and “2 or higher vs. 1”. CI = confidence interval.

In the majority of patients, pulmonary opacification became worse on ECMO support comparing with the baseline (before the ECMO placement). In only 10 cases, there was no deterioration of pulmonary status. In the other 36, lungs became worse on ECMO support, even if the status did not progress to white lungs, and opacification occupied less than half of lung fields. Table 3 shows the numbers and percentages of cases with deterioration, by indication.

In 13 patients, there was decompression of the left ventricle by means of an alternative form of mechanical circulatory support. In eight cases, intraaortic balloon pump was used. Four patients were also on long-term left ventricular assist device (Heartmate II), and one had an Impella 2.5. Because many of the devices were used only for a part of the time on VA ECMO, it would be difficult to derive any conclusions regarding their role in pulmonary congestion.

Specifically, out of 8 cases where intraaortic balloon pump was used, three patients never developed white lungs, but only one of them survived to discharge. Out of those five who had white lungs, only two improved, and one of them survived. Heartmate II was not implanted to decompress the left ventricle, it was already present when patients went on ECMO. None of them survived.

Table 3. Deterioration of pulmonary status on ECMO support, by indication

Indication	Number with indication	Number with deterioration	Percentage with deterioration
Cardiac arrest	14	9	64.3%
Acute myocardial infarction	6	4	66.7%
Heart failure	16	15	93.8%
Pulmonary embolism	1	1	100%
Right ventricular failure	3	3	100%
Postcardiotomy syndrome	5	3	60.0%

The indication for one person was “other”. This person did get worse.

Finally, Table 4 presents p-values for tests of whether the indicated variables are associated with each other. Each measurement of congestion is significantly related to four out of the five outcome or treatment variables.

Table 4. Relationships of congestion measurements to outcomes and treatments

	Duration of support	Survival to ECMO	Survival to discharge	Albumin	Hemodialysis
Average CXR score	p=0.117	p=0.011	p=0.030	p=0.001	p=0.013
Maximal CXR score	p=0.012	p=0.014	p=0.214	p=0.012	p=0.047
White lungs	p=0.015	p=0.015	p=0.019	p=0.086	p=0.033

All outcomes and treatments are significantly related to at least two out of the three measurements of congestion.

Discussion

In our experience, severe degree of pulmonary congestion, with opacification of greater than half of both lung fields is a frequent complication of VA ECMO in adult patients. Specifically, in patients supported on VA ECMO for three days or more, white lungs were present in almost 74% of the cases. This complication

was associated with very high mortality – only 26.5% were discharged alive compared to 66.7% in patients without white lungs.

Longer time of support with VA ECMO, higher ECMO flow, and net fluid balance (both daily and for the duration of VA ECMO support) were associated with higher degree of congestion. Historically, VA ECMO was widely used in the pediatric population. Relatively recently, it has become a commonly used modality for extracorporeal life support in adults in the setting of cardiogenic shock.

Pulmonary congestion is rarely described in ECMO-related literature. The closest term is “left ventricular distension” and there is no uniform way of describing this phenomenon. Some authors suggest that it is diagnosed by echocardiography (1). By default, prevalence and effects of this condition are different than pulmonary congestion diagnosed by CXR. The incidence of left ventricular distension varies widely, ranging from 12-68% (1). However, a review of VA ECMO literature revealed no reports regarding the prevalence of severe pulmonary congestion. In our cohort, the percentage of patients with severe pulmonary congestion was 73.9%. However, only patients supported with VA ECMO for at least three consecutive days were included in this analysis, which likely resulted in a higher incidence of severe pulmonary congestion than that of all patients supported with VA ECMO. As we found, duration of support is directly related to severity of pulmonary congestion. Recently, positive fluid balance while on ECMO support was reported to be an independent predictor of hospital and 90-day mortality (2).

Extreme degree of pulmonary congestion, which we referred to as white lungs, is inconsistently reported. In the US ECLS registry (https://www.elso.org/Registry), this complication is not listed, and therefore is not systematically reported and analyzed. Pulmonary hemorrhage, which is listed as a complication in the registry, probably overlaps with the phenomenon we refer to as white lungs, but is a distinct and different clinical entity.

Meanwhile, we found that white lungs is a common and serious complication, and is associated with high mortality. Per our data, patients who do not experience critical pulmonary opacification survive to discharge in 66.7% cases; survival is only 26.5% in patients who develop white lungs.

There are several potential mechanisms contributing to development of white lungs, which include but are not limited to the following:

- Increased left ventricular end-diastolic pressure due to retrograde ECMO flow into the ascending aorta in central cannulation or femoral artery in peripheral cannulation

- Increased left ventricular afterload due to increased systemic pressure (considering that prior to VA ECMO initiation, patients were in cardiogenic shock with low systemic pressure)
- High pulmonary venous return to the left atrium due to intrinsically high collateral flow from the bronchial circulation to the pulmonary circulation (1)
- The failure of the aortic valve to open due to either the severity of LV impairment or the presence of excessively high systemic vascular resistance imposing a high afterload (1)
- Aortic insufficiency (1)
- High ECMO flow (3)

Interestingly, in an animal model in which five pigs were supported with different rates of ECMO flow ranging from 1 to 5 L/min, increased flow resulted in decreased cardiac output. Cardiac output decreased form 2.8 +/- 0.3 L/min to 1.86 +/- 0.53 L/min ($P < 0.001$) and left ventricular ejection fraction decreased from 43 +/- 3 % to 32 +/- 3 % ($P < 0.001$). LV end-systolic volume also increased. Surprisingly, left ventricular end-diastolic pressure and volume were not significantly affected.(4)

At our institution, we did not consistently use any particular strategy to decompress the left ventricle. Anecdotally, we used hemofiltration, diuretic drips, Impella, and intraaortic balloon pump. Several patients were on left ventricular support at the same time. However, each of the methods was used in very few cases, and no statistical analysis could be justified.

In the literature, various strategies of left ventricular decompression have been proposed:

- Intravenous diuresis. We were anecdotally successful with furosemide drip at 2.5 mg/hour An attempt to use a higher dose led to line chattering and instability of the ECMO circuit.
- Ultrafiltration via the ECMO circuit or via separate access (1)
- Intraaortic ballon pump (1)
- Percutaneous blade or balloon septostomy (5)
- Pigtail catheter, introduced in the left ventricle through the aortic valve, connected to the venous drainage inserted in the femoral artery contralateral to the arterial cannula (6)
- Impella (7, 8)

Other options regarding surgical or percutaneous decompression of the left ventricle are discussed in detail in a review by Rupprecht et al.(3). Left ventricular decompression for the treatment of refractory cardiogenic shock and lung failure brings high success rate and should be utilized early in the care of patients on VA ECMO (9).

Limitations

Our study is limited by retrospective nature of the analysis. Data were recorded in the charts for clinical needs, and some variables had missing values. Also, because we were interested in the phenomenon of severe pulmonary congestion, we intentionally limited the patient population to those who were on support for at least three consecutive days, and therefore increased the representation of this phenomenon.

The groups with white lungs and no white lungs were very uneven, and this could result in no statistically significant differences in some parameters.

Conclusions

Severe pulmonary congestion or white lungs is common in patients on VA ECMO and is associated with a very poor prognosis. Longer duration of support, greater positive fluid balance, higher ECMO flow, and use of hemodialysis are linked to development of white lungs.

Institutions using VA ECMO in adult patients should pay particular attention to the prevention and treatment of white lungs. Measures taken to prevent or treat white lungs can include but are not limited to maintenance of a net negative fluid balance, use of lower ECMO flows, and mechanical decompression of the left ventricle.

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