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Effect of pre-ECMO mechanical ventilation duration on patient outcomes

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Abstract

The majority of the critically ill patients who are treated with extracorporeal membrane oxygenator (ECMO), are initially supported by mechanical ventilation (MV). The pre-ECMO MV duration of more than 7 days was identified as a contraindication to start ECMO support. This study aims to assess the mortality rate in relation to duration of mechanical ventilation before ECMO initiation, as well as its impact of ECMO successful weaning in Saudi Arabia. This is a retrospective cohort study with 13 patients enrolled, who received ECMO support from 2015 to 2019 for both cardiac and non-cardiac indications. All relevant data regarding the MV and ECMO support were extracted and analysed. The whole sample showed a higher mean interval between intubation and ECMO initiation in the successfully weaned group than the group with unsuccessful weaning, with a P value > 0.05. In terms of survival, both groups showed similar MV to ECMO initiation. Total ECMO duration was 10.38 ± 6.55 and 7.60 ± 10.11 for the successful and non-successful weaning groups, respectively (P = 0.56), and was similar for survivors and non-survivors (P = 0.97). Analysis of both subgroups of venovenous ECMO and veno-arterial ECMO was non-significant, both in terms of survival and successful weaning. The pre-ECMO MV duration was significantly higher in patients who were supported by ECMO for more than one week, with a mean duration of 4.50 4.04, in comparison to 1.0 for patients with ECMO support of less than a week (P value=0.041). The impact of pre-ECMO MV duration was not significantly related to ECMO outcomes, including survival and successful weaning, in both ECMO subgroups. However, it may affect the total ECMO support duration.

Keywords: Cardiac, ECMO, Mechanical ventilation, Retrospective, Saudi.

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1. Introduction

Extracorporeal membrane oxygenation (ECMO) is life life-assisting device that provides temporary cardiac and respiratory support to critically ill patients. Veno-venous ECMO (V-V ECMO) mode simulates the lung function by extracting the venous blood, oxygenating it and reinfusing it in the venous system. A similar mechanism is provided by venovenous ECMO (V-A ECMO), however, with the re-infusion of the blood into the arterial system, relieving the overload on the cardiac function [1, 2].

ECMO initiation is still controversial; it is mainly used depending on the patient's response to conventional therapy. For example, in patients with acute respiratory distress syndrome (ARDS), the initial therapy starts with mechanical ventilation (MV), however, if no response is observed, ECMO is initiated to support as well as to avoid MV-induced lung injuries. Similarly, V-A ECMO is initiated in case of bridging to heart and lung transplants or in case of bypass weaning failure post cardiac surgeries [3].

The majority of the critically ill patients who are treated with ECMO are initially supported by MV, which provides the lungs with cyclical ventilation and oxygenation. The pre-ECMO MV duration of more than 7 days was identified as a contraindication for starting ECMO support. Some studies reported that the duration of MV is associated with lower rates of survival in patients supported with VV-ECMO. This can be explained by the possible impact of MV on the pulmonary compliance and alveolar function. Therefore, this study aims to assess the mortality rate in relation to the duration of mechanical ventilation before ECMO initiation, as well as its impact of ECMO on successful weaning in Saudi Arabia.

2. Methods

2.1. Ethical statement

This study was approved by the institutional Research Ethics Board at Imam Abdulrahman bin Faisal University with permit no. IRB-2019-01-316. Data collected at King Fahd Hospital of the University data base, followed by analysis after de-identification of the patients enrolled.

2.2. Study design and patients

This is a retrospective Cohort study conducted by the Cardiac Surgery Unit at King Fahd Hospital of the University. All the adult patients who underwent Extracorporeal membrane oxygenation support of both types, Veno-Venous and Veno-arterial, were enrolled, from the first case done in 2015 till the initiation date of this study in 2019.

2.3. Data Collection

A different range of retrospective data was obtained from the hospital database, including patients' demographics such as age, gender, Body Mass Index (BMI), pre-existing conditions and primary diagnosis. ECMO management-related data, including indications, mode of ECMO, duration of ECMO support, outcomes and complications, were collected. Successful ECMO weaning was defined as the ability to be weaned from the ECMO machine without any significant hemodynamic deterioration for 48 hours after decannulation. The duration of Mechanical Ventilation support before ECMO till cannulation was obtained by reviewing patients' charts and Chest X-rays.

ECMO has been initiated by the cardiac surgery unit, with percutaneous cannulation, whether in the operating room after failure to wean from the cardiopulmonary bypass machine or in the Intensive Care Unit for other indications. The standard ECMO configuration for full support of respiratory failure was venovenous ECMO when cardiac function is adequate or moderately depressed, and veno-arterial in case of depressed cardiac function. V-V access may be by femoral and jugular veins with 2 cannulas or a double lumen cannula via the jugular vein, and with the femoral artery in case of VA access. The standard circuit used included a blood pump, a membrane lung (Oxygenator), and conduit tubing. With additional components like monitors, alarms and heat exchangers as applicable. We used centrifugal pumps, which were capable of providing a flow rate of at least 60-80 ml/kg/min (3-5L/min in all patients). The gas exchange material in membrane lungs may be solid silicone rubber, a microporous hollow-fibre (polypropylene), or a solid hollow-fibre membrane (PMP, polymethyl pentene). The number of oxygenators depended on their maximal O2 delivery at rated flow to match the required blood flow. Continuous hemofiltration (CVVHD) can be added to the circuit if pharmacologic diuresis is inadequate. Anticoagulation using regular or unfractionated heparin to be given as a bolus (50-100 units per kilogram) at the time of cannulation, then continuous intravenous infusion and dose-titrating to maintain a target of activated clotting time (ACT) of 120–140 s. Ventilator settings used during ECMO under sedation: Pressure-controlled ventilation at 25/15, I:E 2:1, rate 5, FiO2 50% ,FiN2 50% . With goal of management is to use FiO2 <0.4, and nondamaging "rest settings (PPlat<25)". PEEP can be as high as tolerated (avoiding inhibition of venous return). ECMO was continued until lung recovery and support is less than 30% of total (as native heart or lung function may be adequate to allow coming off), or until irreversible multi-organ failure leading to death. The weaning process started with decreasing flow in steps to 1L/ min at sweep FiO2 100% OR decreasing flow to 2L/min then decreasing sweep FiO2 to maintain SaO2 > 95%. When SaO2 is stable on these settings, on VV, trial off by clamping sweep on vent rest settings, PSV or spontaneous breathing at 50% FiO2. If SaO2 >95 and PaCO2 <50 for 60 minutes, the trial off is considered successful. Decannulation was performed whenever the patient was ready, but ideally after the heparin had been turned off for 30 to 60 minutes.

2.4. Statistical Analysis

Descriptive statistics were used to describe patients' demographics and clinical characteristics. Continuous data were presented as mean and standard deviation, with categorical data presented as frequencies and percentages. Chi-Square test were used to compare categorical variables between two groups, whereas Student t test or Mann-Whitney U test was used to compare continuous variables between the two groups. A p-value of <0.05 was considered statistically significant. The data were analysed using SPSS (Statistical Package for the Social Sciences, version 16, Inc., Chicago, IL, USA).

3. Results

A total of 13 patients received ECMO during the period of the study. As listed in Table 1, the mean age for patients enrolled was 43.7 ± 9.6. Eight out of 13 were males (61.5%), and 5 of them were females (representing 38.5%). Mean Body Mass Index was 28.9 ± 8.4 kg/m2. In comparison between the successfully weaned group and non-successfully weaned group, both the average age and BMI were similar with p-value >0.05 (44.6 ±8.47 and 42.4 ±11 years respectively) and (26.3 ± 5.4 and 32.6 ± 12.36 kg/m2 respectively). Pre-existing conditions were reviewed in Table 1.

Indications for ECMO initiation were categorised into two groups: cardiac indications, including cardiogenic shock, cardiac arrest and failure to wean from cardiopulmonary bypass, and non-cardiac indications such as respiratory failure. Cardiac indications represent 61.5 % of the total study sample, whereas 38.5% were of non-cardiac indications. (Table 2).

All patients were mechanically ventilated, 12 out of 13 patients were ventilated for less than 7 days and the total ECMO support duration of 8.9 ± 7.7 days. Seven of them were successfully weaned, and four of them died on ECMO. Only one patient was ventilated for 12 days before initiation of ECMO support, with a total ECMO duration of 14 days followed by successful weaning.

Table 1.
Baseline Characteristics of The Patients.

Variable	Value
Age	43.7 ± 9.6
Sex M/F	8 (61.5%)/5(38.5%) 28.9 ± 8.4 2 (15.3%)
BMI	4 (30.7%)
Coronary artery disease	9 (69%)
Diabetes	4 (30.7%)
Hypertension	1 (7.7%)
Dyslipidemia	2 (15.3%)
COPD	1 (7.7%)
Chronic kidney disease	1 (7.7%)
Aortic dissection	1 (7.7%)
Hodgkin lymphoma	1 (7.7%)
CNS tb	1 (7.7%)
Inflammatory bowel	1 (7.7%)
syndrome	1 (7.7%)
Sickle cell disease	1 (7.7%)
Heavy smoker	1 (7.7%)
post mechanical valve	1 (7.7%)
implantation	1 (7.7%)
Pregnancy	1 (7.7%)
No pre-existing condition	1 (7.7%)

Table 2.
Indications of Extracorporeal Membrane Originator.

Indication	Frequency (n)	Percentage (%)
Respiratory failure	5	38.5
Cardiogenic shock	2	15.3
Cardiac arrest	4	30.7
Failure to wean from bypass	2	15.3

Table 3.
Outcomes of Patients on ECMO Support According to Pre-ECMO MV Interval and Total ECMO.

Characteristics	Successful Weaning	Unsuccessful Weaning	P Value	Survivors	Non Survivors	P Value
Pre-ECMO MV duration	3.25 ± 3.88	1.60 ± 1.38	0.39	2.40 ± 1.95	2.75 ± 3.88	0.86
Total EC MO duration	10.38 ± 6.55	7.60 ± 10.11	0.56	9.20 ± 7.36	9.38 ± 8.58	0.97

Table 4.
Outcomes of Patients on ECMO Support According to Pre-ECMO MV Interval in subgroups of ECMO.

Characteristics	Successful weaning	Unsuccessful weaning	P value	Survivors	Non-Survivors	P value
V-V ECMO (n=6)	2.75± 2.06	2.50 ± 2.12	0.89	2.75 ±2.06	2.50 ± 2.12	0.89
V-A ECMO (n=7)	3.75±5.50	1 ± 0	0.44	1 ±0	2.83 ± 4.49	0.6

Table 5.
Outcomes of Patients on ECMO Support According to Total ECMO Duration in subgroups of ECMO.

Characteristics	Successful weaning	Unsuccessful weaning	P value	Survivors	Non-Survivors	P value
V-V ECMO (n=6)	11.25 ± 6.65	13.50 ±16.26	0.81	11.25 ± 6.65	13.50 ± 6.26	0.81
V-A ECMO (n=7)	9.5 ± 7.33	3.67 ±3.79	0.27	1 ± 0	8±4.2	0.19

Table 6.
Correlation Between Pre-ECMO Mechanical Ventilation and Total Duration of ECMO Support.

Characteristics	ECMO Support ≤7	ECMO Support >7	P value
Pre-ECMO mechanical Ventilation Duration	4.50±4.04	1±0.01	0.04

Analysing the outcomes for the whole sample showed a mean interval between intubation and ECMO initiation of 3.25 ± 3.88 days in the successfully weaned group and 1.60 ± 1.38 days in the group with unsuccessful weaning, with p value = 0.39.

Comparing the MV-ECMO interval between the two groups of survivors and non-survivors showed mean days of 2.40 ± 1.95 and 2.75 ± 3.88, respectively, with a p value = 0.86 (Table 3).

V-V ECMO group with successful weaning showed a mean interval of 2.75 ± 2.06, which is lower than the mean interval for the V-A group, with a mean interval of 3.75 ± 5.50 and P value of 0.75. Table 4 shows the mean interval between MV and ECMO in terms of survival and successful weaning in both subgroups of V-V ECMO and V-A ECMO.

Regarding the total ECMO duration, the mean was 10.38 ± 6.55 and 7.60 ± 10.11 for successful and non-successful weaning, respectively, with P value = 0.56, and similar duration for survivors, 9.20 ± 7.36 and non-survivors of 9.38 ± 8.58 with P value =0.97. (Table 3). In the analysis of subgroups of ECMO, V-V ECMO showed a shorter duration of ECMO in the successful weaning group, 11.25 ± 6.65, than the non-successful weaning group,13.50 ±16.26, with a P value =0.81, and similar results between the survivors and non-survivors. V-A ECMO group also showed a shorter duration of ECMO, both in terms of survival and successful weaning (Table 5).

The pre-ECMO mechanical ventilation duration was significantly higher in patients who were supported by ECMO for more than one week, with a mean duration of 4.50 4.04, in comparison to 1 0 for patients with ECMO support of less than a week, with p p-value of 0.041 (Table 6).

The complications reported in the study sample that related to ECMO access included wound infection, bleeding from the ECMO access site and limb ischemia that ended in amputation. Other unfortunate outcomes included spontaneous abortion and spontaneous pneumothorax.

4. Discussion

Patient outcomes after ECMO have been studied since its implementation. Many scores, such as the RESP and ECMOnet scores, have been developed to predict ECMO outcomes based on patients' conditions before starting ECMO support. Lactic acid level, immunocompromised state and SOFA score are known as predictors of worse outcomes post-ECMO [4].

One of the important observations predicting the outcomes in patients treated with ECMO is the duration of mechanical ventilation before starting ECMO support. The mechanical ventilation works by providing the lung with cyclical ventilation and oxygenation [5]. Ventilators may induce lung injury through multiple mechanisms if not managed properly, which includes what is known as barotrauma, which results from the high ventilatory pressure which ultimately causes alveolar air leak. Moreover, the high volume of the lung causes hyperdistention of the alveoli, leading to increased alveolar-capillary permeability and pulmonary oedema. The cyclical ventilation may also contribute to high shearing forces resulting from the repetitive opening and closing of the alveoli; in addition, it may trigger proinflammatory mediators that induce pulmonary injury [6, 7].

The presented protocol for ECMO initiation identifies the duration of mechanical ventilation of more than 7 days as a contraindication for ECMO support initiation. The exact effect of prolonged MV on ECMO outcomes is unknown; however, it can be explained by the negative impact of MV on pulmonary physiology. Different studies reported different MV to ECMO intervals in terms of survival, with significant correlations. A retrospective study done in China reported a significant increase in pre-ECMO ventilation time in non-survivors of ARDS in comparison to survivors. The average duration of pre-ECMO MV was 3 days in surviving patients compared to 8 days in non-survivors [8]. One day in survivors and 6 days for non-survivors according to a study done by Wu, et al. [9]. These results are similar to what was reported by Schmidt in a comprehensive follow-up study for ECMO patients who were treated for ARDS. They followed their patient for six month duration and analysed all the factors in relation to mortality. They recognised the pre-ECMO mechanical

ventilation of more than 6 days to be associated with decreased post-ECMO six month's survival rates. The median pre-ECMO mechanical ventilation was 3 days in survivors, whereas seven days in non-survivors [10]. These studies reported a mean of 3 days to be a predictor of survival in V-V ECMO, which is similar to the mean interval in survivor patients in this study; however, the non-survivors also had a similar interval. Other studies reported similar intervals between survivors and non survivors; Roch, et al. [11] reported median of 2 days for both groups in term of survival, Serpa Neto, et al. [12] found median of 2 and 3 days for survivors and non-survivors respectively, in addition to Wu, et al. [13] and Pappalardo, et al. [14] whom found median of less than two days in both groups.

On the other hand, there is small number of patients who were ventilated for more than 7 days and were successfully weaned from ECMO, which may indicate the possible benefits of ECMO in prolonged ventilated patients if the barotrauma is excluded [8]. In the study, only one patient out of 13, was ventilated for 12 days before initiating VA ECMO, with a total ECMO duration of 14 days followed by successful weaning. For the remaining patients, pre-ECMO mechanical ventilation was less than 7 days, with different outcomes not statistically related to mortality or successful weaning.

Another correlation had been described between the impact of the mechanical ventilation before initiating ECMO support on the total ECMO duration. A study done by Na, et al. [15] found that the duration of pre-ECMO MV was significantly associated with the total ECMO duration. This is compatible with the findings of this study, with a mean MV to ECMO interval of 1.0 for patients supported by ECMO for a week or less, and 4.5 4.0 for patients who were on ECMO for more than a week, with a significant P value of 0.041

The mechanism of MV ultimately will cause a decrease in the pulmonary compliance (PC). Pre-ECMO pulmonary compliance has been reported to have a significant impact on the survival rate and outcomes, which may be used to identify the possible damage caused by the MV. PC of less than 20 ml/cmH2O was associated >25% risk of mortality. These observations indicate the possibility of using pre-ECMO pulmonary compliance as a predictor of mechanical ventilation-induced lung injuries, therefore, predicting the outcomes of using ECMO support.

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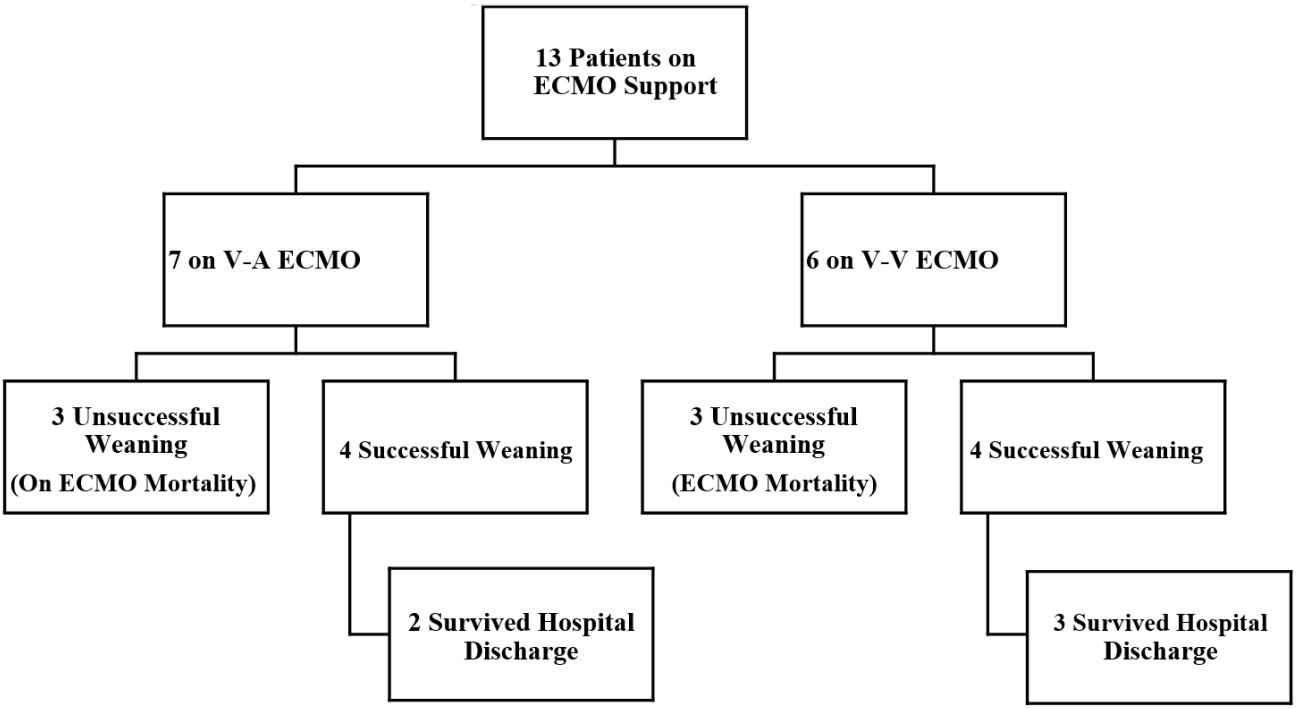

Figure 1.
Flowchart of the study sample outcomes. ECMO; extracorporeal membrane oxygenation. VV ECMO; Veno-venous extracorporeal membrane oxygenation. VA ECMO; Veno-Arterial extracorporeal membrane oxygenation.