Bicarbonate in Arteries Measured Preoperatively for Cadaveric Single-lung Transplantation is Related to Intraoperative Extra-Corporeal Membrane Oxygenation Use: A Retrospective Preliminary Study

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ABSTRACT

Background: There are no known predictors of extracorporeal membrane oxygenation (ECMO) induction for single lung transplantation.

Objective: The purpose of the present study was to clarify the relationship between variables and ECMO requirements in single lung transplantation.

Methods: This study included adult patients who underwent cadaveric single lung transplantation between 2010 and 2019. After general anesthesia, the transplanted lungs were ventilated in all cases. The analysis included 38 patients in the ECMO required (RQ) group and 12 patients in the ECMO non-required (FR) group. Comparisons were made between the two groups for data affecting ECMO implementation, and data that were significantly different were subjected to multivariate analysis.

Results: Prior to anesthesia, the bicarbonate (HCO_3-) value of the FR group was lower than that of the RQ group (24.6±2.7 vs. 29.7±5.3 mmol/L, p=0.005). Multivariate analysis showed that the cut-off bicarbonate value was 29.6. The area under the receiver operating characteristic curve (AUROC) of the model was 0.869 (R^2: 0.331), with a sensitivity of 79% and a specificity of 88%. The odds ratio was 1.63 for every unit increase in the bicarbonate value (95%CI: 1.11-2.39, p<0.001). Further, the FR group had higher arterial blood pressure (mean: 79.0±11.5 vs. 68.9±8.3 mmHg, p=0.030), less blood loss (432±385 vs. 1,623±1,997 g, p<0.001), shorter operation time (417±44 vs. 543±111 min, p<0.001), and shorter ICU stay (11±9 vs. 25±38 days, p=0.039).

Conclusion: Preoperative evaluation of bicarbonate could predict the need for ECMO for single lung transplantation.

KEYWORDS: Single Lung Transplantation; Extracorporeal Membrane Oxygenation; Retrospective Studies

INTRODUCTION

Single- or double-lung transplantation is an established treatment for end-stage chronic obstructive pulmonary disease or idiopathic pulmonary fibrosis. In Japan, owing to the significantly low number of cadaveric donors, single-lung transplantation is indicated for 40-65% of lung transplants for patients with these diseases, but the results are worse than those of double-lung transplantation (5-year survival rate: 48% vs. 59%) [1-3].

Extracorporeal membrane oxygenation (ECMO) is often used in lung transplant recipients. Most of its purposes are mainly both circulatory and respiratory in double-lung

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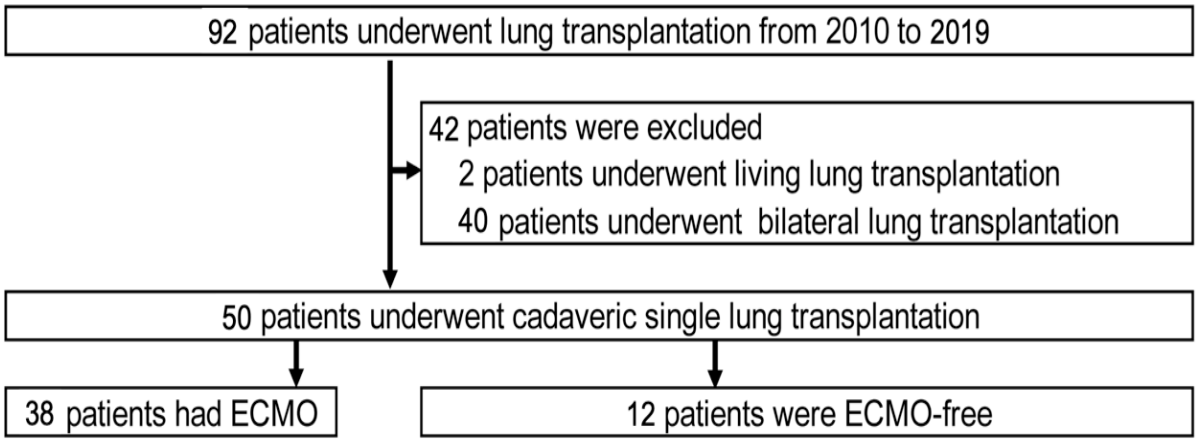

Figure 1: Outline for the assessment of qualified patients.

transplantation and only respiratory in single-lung transplantation. There have been many reports on the criteria for applying ECMO based on circulatory failure, hypoxemia, and right heart failure. However, the use of ECMO increases mortality in patients receiving lung transplants by increasing the probability of bleeding, renal dysfunction, and infection [4-7].

Therefore, it is clear that avoiding the use of ECMO whenever possible can improve the prognosis of patients receiving lung transplants and reduce the associated healthcare costs (8). Furthermore, if there are preoperative predictors of the need for ECMO in these patients, it may be possible to use ECMO before a crisis situation occurs. Therefore, in this exploratory study, we focused on the respiratory factors leading to the application of ECMO in patients undergoing single-lung transplantation.

MATERIALS AND METHODS

Study Design and Population

Patients aged 20 years or older who underwent cadaveric lung transplantation between January 2010 and December 2019 were included. Patients with second or subsequent transplantation were excluded. Patients with history of lung transplantation were included. Eligible patients were divided into an RQ group, including those who required ECMO, and an FR group, including those who did not.

Anesthesia

Prior to general anesthesia, an arterial line was placed in the radial artery under consciousness. Induction drugs were selected from remifentanil, fentanyl, propofol, midazolam, and rocuronium, and maintenance was selected from the same drugs. A double lumen endotracheal tube was used for intubation, confirmed with bronchoscopy. A central venous catheter and pulmonary catheter were inserted in the internal jugular vein. A transesophageal echocardiographic probe was also inserted in all patients. The decision to apply ECMO was made in consultation with the anesthesiologist and surgeon according to four criteria (4): circulatory failure (cardiac index below 2 L/min/m2), hypoxemia (PaO_2 <60 Torr or SpO_2 <90%), hyperventilation ($PaCO_2$ >60 Torr or $ETCO_2$ >60 mmHg), and right heart failure (pulmonary blood flow ratio >0.9). If these criteria were observed even during surgery, ECMO was to be introduced after suspending the surgery. The intraoperative position was right-lateral for left-sided lung transplantation and supine for right-sided lung transplantation.

Endpoint

ECMO implementation was the primary endpoint of this study.

Data Collection

All data for the study were extracted from electronic medical records and the anesthesia department system. The personal information was consolidated and anonymized before the start of the study. All collectable data such as demographic, laboratory, drug, treatment, and event data for each patient were extracted. All data were subjected to analysis and presented as patient background.

Ethical Consideration

This study was performed after obtaining ethics approval from the postgraduate ethics committee of our institution (1-803, 2018). All patients provided written consent to enter the study.

Statistical Analysis

Predictors were analyzed in the RQ and FR groups. Continuous data were analyzed with the Wilcoxon rank sum test. Binary comparisons were performed with Fisher's exact test. Multiple logistic regression analysis was used for variables with significant differences. Power analysis was performed using post-hoc analysis. Multicollinearity was assessed based on whether the variance inflation coefficient exceeded 10, and the fit to the linear gradient was checked graphically (9). Logarithmic transformations and polynomials were performed as needed. The criterion for statistical significance was set at $p<0.05$. All analyses were performed using JMP® 15.0 (SAS Institute Inc., Cary, NC).

RESULTS

We analyzed the data of 50 patients who met the inclusion criteria. The patient selection flowchart is shown in Fig 1, and patients' characteristics are shown in Table 1. All ECMO was performed in the operating room; 25 patients received venoarterial ECMO (two of the cases migrated during surgery), 14 patients received veno-venous ECMO, and one patient was intraoperatively switched from venoarterial to veno-venous ECMO. Thirty-eight patients (76%) were included in the RQ group, and the remaining 12 patients (24%) were included in the FR group. There was one case of intraoperative tension pneumothorax in the FR group, but ECMO was not necessary.

In the pre-anesthetic evaluation, the PaCO2 (39.1±6.6 vs. 48.5±14.2 mmHg, p=0.029) and bicarbonate (24.6±2.7 vs. 29.7±5.3 mmol/L, p=0.005) values were significantly lower in the FR than in the RQ group. After the introduction of anesthesia, only the bicarbonate value was significantly lower in the FR group (26.5±3.7 vs. 30.8±5.1 mmol/L, p=0.009). None of the blood gas analysis data, including other oxygenation indices, were significantly different. Blood pressure immediately before the start of surgery was significantly higher in the FR group (mean: 79.0±11.5 vs. 68.9±8.3 mmHg, p=0.030. diastolic: 60.1±8.2 vs. 53.1±7.0, p=0.039).

We performed a multivariate analysis on the predictors that were significantly different (Fig 2). The area under the receiver operating characteristic curve (AUROC) of the prediction model was 0.869 (R^2: 0.331), with a sensitivity of 79% and a specificity of 88%. The odds ratio was 1.63 for every 1-point increase in the bicarbonate value (95%CI: 1.11-2.39, $p<0.001$) (Table 2). There was no multicollinearity among the variables in the prediction model. In the post-hoc analysis, the power was 0.368. The distribution of bicarbonate values is shown in Fig 3.

In terms of outcomes (Table 1), the FR group experienced less blood loss (432±385 vs. 1,623±1,997 g, $p<0.001$), shorter operative time (417±44 vs. 543±111 min, $p<0.001$). The number of days spent in the intensive care unit (ICU) was also significantly lower (11±9 vs. 25±38 days, p=0.039).

DISCUSSION

In this study we examined preoperative factors related to the use of ECMO in single-lung transplantation and suggested that the bicarbonate value in arterial blood is an appropriate predictor. Seventy-six percent of the patients who received single-lung transplantation underwent ECMO, indicating that most of them

Table 1: Patients' characteristics.

Variables	ECMO-free (n= 12)	ECMO use (n= 38)	P value
Age (years), (mean±SD)	49.3 ± 11.7	52.4 ± 9.2	0.212
Female, no. (%)	7 (58.3%)	26 (68.4%)	0.728
Body mass index, (mean±SD)	20.8 ±5.3	20.5 ±6.1	0.625
Primary disease, no. (%)			
Lymphangioleiomyomatosis	5 (41.7%)	19 (50.0%)	
Emphysema	2 (16.7%)	2 (5.3%)	
Idiopathic interstitial pneumonia	2 (16.7%)	9 (23.7%)	
Secondary interstitial pneumonia	2 (16.7%)	4 (10.5%)	
Idiopathic pulmonary fibrosis	0 (0.0%)	2 (5.3%)	
Others	1 (8.3%)	2 (5.3%)	
Previous chest surgery, no. (%)	2 (16.7%)	6 (15.8%)	1.000
Flow rate of home oxygen therapy (L/min), (mean±SD)	2.5 ± 2.0	3.0 ± 1.7	0.212
Transthoracic echocardiography, (mean±SD)			
Left ventricular ejection fraction (%)	64.8 ± 11.9	64.5 ± 6.2	0.622
Trans-tricuspid pressure gradient (mmHg)	24.1 ± 8.0	26.4 ± 8.5	0.744
Ventilation perfusion ratio of dependent lung	0.4 ± 0.2	0.5 ± 0.1	0.801
Lung grafts			
Ischemic interval (min), (mean±SD)	428.8 ± 60.2	464.3 ± 58.5	0.172
Right side, no.(%)	7 (58.3%)	17 (44.7%)	0.514
Blood Gas Analysis[a]			
Before induction of general anesthesia			
pH, (mean±SD)	7.417 ± 0.031	7.408 ± 0.045	0.650
PaO2 (mmHg), (mean±SD)	159 ± 82	147 ± 83	0.873
FiO2, mean (SD)	0.45 ± 0.22	0.40 ± 0.19	0.542
PaO2/FiO2 ratio, (mean±SD)	398.2 ± 146.6	383.5 ± 190.4	0.325
PaCO2 (mmHg), (mean±SD)	39.1 ± 6.6	48.5 ± 14.2	0.029*
HCO_3- (mmol/L), (mean±SD)	24.6 ± 2.7	29.7 ± 5.3	0.005**
After induction of general anesthesia			
pH, (mean±SD)	7.321 ± 0.049	7.281 ± 0.103	0.256
PaO2 (mmHg), (mean±SD)	385 ± 125	276 ± 120	0.029*
FiO2, (mean±SD)	0.96 ± 0.13	0.86 ± 0.19	0.155
PaO2/FiO2 ratio, (mean±SD)	382.8 ± 101.0	318.3 ± 144.9	0.330
PaCO2 (mmHg), (mean±SD)	53.5 ± 10.7	71.2 ± 28.4	0.051
HCO_3- (mmol/L), (mean±SD)	26.5 ± 3.7	30.8 ± 5.1	0.009**
Vital Sign Data of Preoperation[b]			
Systolic arterial pressure (mmHg), (mean±SD)	102.2 ± 15.5	94.1 ± 13.3	0.132
Diastolic arterial pressure (mmHg), (mean±SD)	60.1 ± 8.2	53.1 ± 7.0	0.039*
Mean arterial pressure (mmHg), (mean±SD)	79.0 ± 11.5	69.0 ± 8.4	0.038*
Systolic pulmonary arterial pressure (mmHg), (mean±SD)	43.9 ± 14.6	41.7 ± 13.8	0.485

Table 1: Continued.

Central venous pressure (mmHg), (mean±SD)	9.0 ± 3.1	8.4 ± 3.2	0.837
Mixed venous oxygen saturation (%), (mean±SD)	81.5 ± 7.9	82.1 ± 7.2	0.897
Results of Operation			
Operative time (min), (mean±SD)	417 ± 44	543 ± 111	< 0.001**
Bleeding (g), (mean±SD)	432 ± 385	1623 ± 1997	< 0.001**
Outcomes			
Inhaled nitric oxide therapy (days), (mean±SD)	4 ± 4	9 ± 14	0.080
Mechanical ventilation (days), (mean±SD)	8 ± 8	20 ± 40	0.076
Length of ICU stay (days), (mean±SD)	11 ± 9	25 ± 38	0.039*
Length of hospital stay (days), (mean±SD)	80 ± 24	121 ± 192	0.207
ECMO			
V-A ECMO, no.(%)[c]	None	25 (75.8%)	
V-V ECMO, no.(%)[c]	None	14 (36.8%)	
Duration of therapy (days), (mean±SD)	None	1.9 ± 2.4	

Results are presented along with standard deviations (±). Analyses were performed using Wilcoxon and Fisher's exact tests. *: P<0.05, **: P<0.01. ECMO: extra-corporeal membrane oxygenation, ICU: intensive care unit, V-A: veno-arterial, V-V: veno-venous.

[a]Arterial blood gas analysis data sampled during the period after the induction of general anesthesia to the start of surgery.

[b]Vital sign data at the insertion of a pulmonary artery catheter after induction of the general anesthesia and before starting the operation.

[c]One case was switched from V-A ECMO to V-V ECMO during surgery.

could wean-off on the day of surgery (median: 1 day). Nevertheless, the use of ECMO was associated with increased intraoperative blood loss, longer operative times, and significantly longer ICU stay, suggesting that the impact on the outcome was considerable.

The current study design had the issue that the CO2 concentration in patients changes depending on the ventilator setting, making it inappropriate as a predictor. On the other hand, bicarbonate is controlled by the metabolism and is not easily affected by ventilator settings. Therefore, bicarbonate measured not long after induction of general anesthesia may reflect relatively accurately the respiratory state before anesthesia.

In the multivariate analysis, a bicarbonate value of 29.6 mmol/L was found to be a cutoff value as a predictor of ECMO induction. From this value, the cutoff for PaCO2 can be obtained by applying the acid–base equilibrium equation [10]:

$$[pH] = 7.4 = 6.1 + \log([HCO_3^-]/(0.03 \times PaCO2))$$

$$PaCO2 = [HCO_3^-]/0.6 = 29.6/0.6 = 49.3 \text{ Torr}$$

The difference between the two groups for the bicarbonate value was small (5.1 mmol/L), but for the PaCO2 value was large (8.5 Torr), which is considered clinically significant indicator.

The RQ group included two cases in which V-A ECMO was introduced intraoperatively on an emergency. In addition, these patients experienced increase in systolic pulmonary arterial pressure to >60 mmHg and a decrease in mean arterial pressure <60 mmHg, which did not respond to medical therapy. In these patients, circulatory failure and right heart failure occurred simultaneously, forcing the unexpected introduction of ECMO. Conversely, given that all patients in the FR group had a preoperative bicarbonate level >29.6 (Fig 3), it may be better not to perform ECMO upfront in patients who meet this criterion.

The limitation of this study is that potential bias (e.g., selection of target diseases, surgical techniques, and predictors) could not be

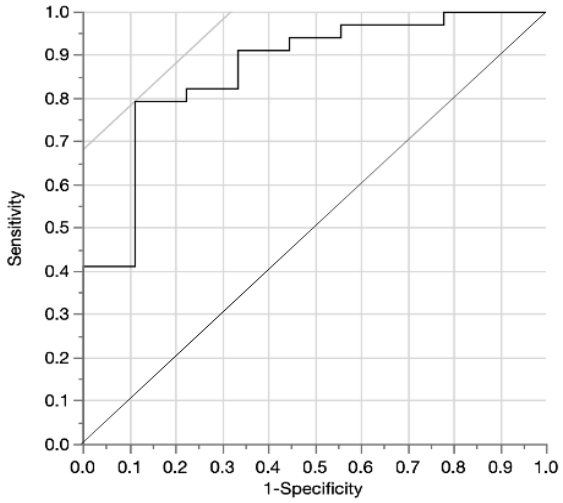

Figure 2: Extracorporeal membrane oxygenation indications predicted from preoperative factors. Multivariate analysis showed that the cut-off value of bicarbonate was 29.6. The AUROC of the model was 0.869 (R^2: 0.331), with a sensitivity of 79% and a specificity of 88%. Statistics were performed using logistic regression analysis.

excluded because it was a single-center retrospective analysis based on a multicenter collaborative study. In addition, the power in multivariate analysis was 0.368, which was not sufficient. A multicenter study with approximately 169 patients is needed to obtain sufficient confidence in the results of this study. In addition, the criteria for the introduction of ECMO were not strict. Future multicenter studies should include patients receiving double-lung transplantation.

Table 2: Risk factors of ECMO indication.

	OR (95% CI)	P value
HCO_3- (+1 mmol/L)	1.63 (1.11-2.39)	<0.001**
MAP (+1 mmHg)	1.13 (1.00-1.27)	0.026*

Statistical analysis was logistic regression analysis. R^2: 0.331, AUROC: 0.869. ECMO: extra-corporeal membrane oxygenation, MAP: mean arterial pressure, OR: odds ratio, CI: confidence interval, AUROC: area under of receiver operating characteristic curve.

In conclusion, evaluation of preoperative bicarbonate value in patients undergoing single-lung transplantation may predict the need for ECMO.

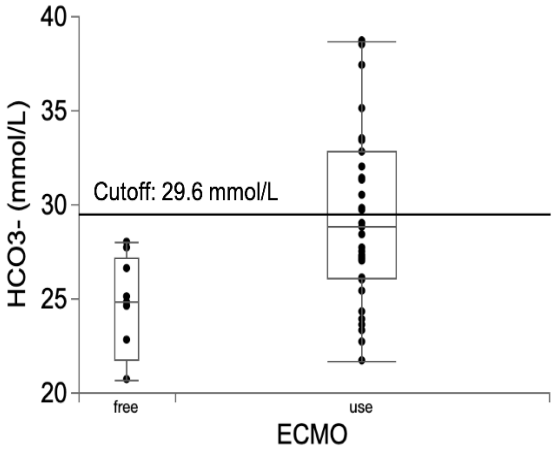

Figure 3: Distribution of bicarbonate before induction of general anesthesia. The cut-off value of bicarbonate was 29.6 mmol/L.

CONFLICTS OF INTEREST: None declared.

FINANCIAL SUPPORT: This work was supported by JSPS KAKENHI (Grant Number 19K18343).

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