Blood lactate level during extracorporeal life support as a surrogate marker for survival

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Objective: The establishment of reliable markers to monitor adequate tissue perfusion during extracorporeal life support is clinically important to improve outcomes.

Methods: We evaluated 115 consecutive adult patients (aged 61.7 ± 13.4 years, 59 female patients) undergoing extracorporeal life support to manage low cardiac output syndrome after major cardiac surgery. The blood lactate levels serially measured during extracorporeal life support (at 6, 12, and 24 hours) were analyzed.

Results: Forty-seven patients (40.8%) were weaned off extracorporeal life support successfully, and 32 patients (27.8%) survived to discharge. On logistic regression analysis, a high blood lactate level before extracorporeal life support (relative risk [RR], 1.19; 95% confidence interval [CI], 1.06-1.34) and cardiopulmonary bypass weaning failure after surgery (RR, 4.39; 95% CI, 1.44-13.35) emerged as baseline risk factors of mortality. After adjustment with these factors, blood lactate levels at 6 hours (RR, 1.24; 95% CI, 1.06-1.46), 12 hours (RR, 1.35; 95% CI, 1.10-1.67), and 24 hours (RR, 1.46; 95% CI, 1.10-1.93) were predictive of mortality. When the predictive values of serial blood lactate levels for mortality were assessed using the receiver operating characteristic method, the greatest accuracy was obtained at cutoff values of 7.05 mmol/L at 6 hours (sensitivity, 75.5%; specificity, 75.0%), 4.95 mmol/L at 12 hours (sensitivity, 70.4%; specificity, 76%), and 4.15 mmol/L at 24 hours (sensitivity, 62%; specificity, 93.1%).

Conclusions: Blood lactate measurement can be used as a reliable tool for monitoring adequate tissue perfusion during extracorporeal life support and was strongly predictive of mortality. Therefore, in patients without adequate decrement in lactate levels during extracorporeal life support, potential factors responsible for inadequate perfusion should be identified and corrected. (*J Thorac Cardiovasc Surg* 2014;148:714-20)

With the technologic advancement of extracorporeal life support (ECLS) and improvement in its management strategies, the use of ECLS has been generalized in clinical practice over the past decade. ECLS can provide total circulatory support with fully oxygenated blood so that systemic tissue perfusion is satisfied in patients with severe respiratory or circulatory failure. Nevertheless, achieving adequate tissue perfusion can be disturbed by unexpected clinical situations, such as device-related problems, cannulation-related complications, and hemorrhagic events. These situations may lead to tissue hypoperfusion and consequent end-organ damage, ultimately hampering the outcomes of ECLS.^{1,2} In these regards, early detection

of suboptimal tissue perfusion despite the ECLS implementation will be clinically important to identify correctable factors of hypoperfusion and thereby to improve the outcomes. Nonetheless, the reliable monitoring markers of adequate tissue perfusion during ECLS have not been established to date.

High lactate level is known to be an independent predictor of low cardiac output syndrome and major complications after cardiac surgery.^{3,4} Blood lactate level can be promptly measured in intensive care unit (ICU) settings from simple arterial blood gas analysis (ABGA) samplings. In this study, we hypothesized that arterial blood lactate level during ECLS can be used as a reliable predictive marker of mortality. Therefore, we sought to evaluate the role of serially measured arterial lactate level during ECLS as a monitoring tool for tissue perfusion in the setting of post-cardiac surgery ECLS.

METHODS

Patients

Between May 2005 and December 2012, 10,197 adult patients underwent major cardiac surgery at the Asan Medical Center, Seoul, Korea. These surgeries included valve surgery, coronary artery bypass grafting, aortic surgery, resection of cardiac tumors, pericardiectomy, pulmonary thromboembolism, and heart transplantation. Of these patients, 125 were supported with venoarterial-type ECLS for low cardiac output

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Abbreviations and Acronyms

ABGA	= arterial blood gas analysis
CI	= confidence interval
CPB	= cardiopulmonary bypass
ECLS	= extracorporeal life support
ICU	= intensive care unit
ROC	= receiver operating characteristic
RR	= relative risk

syndrome after major cardiac surgery at the Asan Medical Center, Seoul, Korea. After exclusion of 10 patients who underwent preoperative ECLS, 115 patients were included in this study. Clinical situations that required postoperative ECLS were as follows: (1) 48 patients with usual postoperative low cardiac output syndrome that was unresponsive to inotropics or intra-aortic balloon pumping, (2) 27 patients with witnessed cardiac arrest that was unresponsive to standard advanced cardiopulmonary life support, and (3) 40 patients with postoperative cardiopulmonary bypass (CPB) weaning failure.

The study was approved by the institutional ethics committee/review board of the University of Ulsan, and the requirement for informed patient consent was waived in view of the retrospective nature of the study.

Extracorporeal Life Support Devices and Management

Venoarterial ECLS was implemented at the common femoral artery and vein or internal jugular vein using the Seldinger technique in all 115 patients. The ECLS system consisted of a centrifugal pump, a hollow fiber membrane oxygenator with an integral heat exchanger, and a heparin-bound circuit. Three types of ECLS system were used: the Capiex Emergent Bypass System (Terumo Corp, Tokyo, Japan) was used for 94 patients (81.7%), the PLS System (Maquet, Hirrlingen, Germany) was used for 14 patients (12.2%), and the Bio-Console 560 System (Medtronic, Inc, Minneapolis, Minn) was used for 7 patients (6.1%).

Blood lactate level measurement was performed routinely every 2 to 3 hours from simple ABGA samples. The ABGA samples were analyzed by GEM Premier 3000 (Instrumentation Laboratory, Lexington, Mass).

An intravenous heparin bolus of 100 U/kg was administered to achieve a celite activated clotting time (measured using a Hemochron 401 machine, Soma Technology, Bloomfield, Conn) of 300 seconds before cannulation of arterial and venous catheter. After the initiation of ECLS, the activated clotting time was maintained within a range of 180 to 200 seconds. From 2010, nafamostat mesilate (Futhan; Torii Pharmaceutical, Tokyo, Japan), a synthetic serine protease inhibitor, was adopted to use as an alternative anticoagulant to heparin for patients with a high risk of bleeding. For these patients, a half-dose of heparin was administered before cannulation, and activated clotting time was maintained within 160 to 180 seconds after the administration of a starting dose of 0.75 mg/kg nafamostat mesilate. The patients ($n = 5$) with severe coagulopathy in the immediate postoperative period were not administered heparin or nafamostat mesilate until the bleeding was controlled. The details of coagulation strategy during ECLS and ECLS weaning protocol have been described.⁵

We tried to maintain the ECLS blood flow greater than the cardiac index of 2.4 L/min/m². To maintain the mean arterial pressure of 60 to 70 mm Hg, vasopressors such as norepinephrine or vasopressin were administered as needed. Red blood cells and platelets were transfused to maintain the hematocrit of 30% to 35% and platelet count greater than $100 \times 10^3/\text{mm}^3$ for patients with a high bleeding risk. An antegrade perfusion catheter for distal limb perfusion was routinely placed distal to the arterial cannulation site, except in the case of the failure to implant the catheter because of technical difficulties.

Statistical Analysis

Categorical variables are presented as frequencies and percentages, and were compared using the Chi-square test or Fisher exact test. Continuous variables are expressed as mean $\pm$ standard deviation and were compared using the Student unpaired *t* test. To determine the baseline risk factors for mortality, logistic regression models were used. At the first stage of the analyses, baseline characteristics of patients and variables related to ECLS were considered in the logistic regression model. Variables with a *P* value of .20 or less in univariable analyses were candidates for the multivariable models. Multivariable analyses involved a backward elimination technique, and only variables with a *P* value of .10 or less were used in the final model. To evaluate the impact of post-ECLS lactate level on death, further multivariable analyses were conducted that involved serial post-ECLS lactate levels at each point and significant variables affecting mortality in the second stage of the analyses. Results were expressed as a relative risk (RR) with 95% confidence intervals (CIs). The predictive value of post-ECLS lactate level for mortality was evaluated by analyzing areas under receiver operating characteristic (ROC) curves, with their 95% CI. The optimal cutoff value corresponded to the value with the greatest accuracy. Survival was estimated by the Kaplan-Meier method and compared by the log-rank test. All reported *P* values are 2-sided. Statistical analyses were performed with SPSS 18.0 for Windows Software (IBM, Armonk, NY).

RESULTS

The baseline characteristics and clinical data related to ECLS of the patients are shown in [Tables 1 and 2](#), respectively. The patients who died in-hospital required a longer CPB time during surgery and were more likely to undergo ECLS at the end of the operation because of CPB weaning failure than those who survived to discharge, whereas there were no significant differences between the 2 groups in other baseline profiles. The levels of arterial blood lactate before and after the initiation of ECLS were significantly higher in patients who died in-hospital compared with those in the group of survivors to discharge.

Sixty-three patients (54.8%) experienced at least 1 complication during ECLS. [Table 3](#) provides the details of complications that occurred during ECLS. The serial blood lactate levels at 6 hours (9.73 ± 4.48 vs 7.01 ± 4.39 ; $P = .007$), 12 hours (8.10 ± 4.76 vs 5.14 ± 3.74 ; $P = .003$), and 24 hours (6.48 ± 4.98 vs 4.00 ± 2.92 ; $P = .008$) after ECLS initiation were significantly higher in the patients who had at least 1 complication ($n = 63$) than the patients without complications ($n = 52$). The incidence rates of overall complications were significantly higher in patients who died in-hospital than those who survived to discharge ($P = .003$).

The overall outcomes of ECLS are summarized in [Figure 1](#). Two patients underwent successful heart transplantation and survived to discharge. Forty-seven patients (40.8%) were weaned off ECLS successfully; however, 17 patients died after successful weaning from ECLS in-hospital. The cause of death after successful weaning was multiple organ failure in 6 patients, profound cardiac failure in 3 patients, sepsis in 2 patients, pan-peritonitis in 2 patients, aortic rupture in 2 patients,

TABLE 1. Baseline characteristics of patients who underwent extracorporeal life support after major cardiac surgery

Variables	Total (n = 115)	Discharged (n = 32)	Died in-hospital (n = 83)	P value
Age, y	61.7 ± 13.4	58.2 ± 16.1	63.0 ± 11.9	.088
Male gender, n (%)	56 (48.7)	16 (50)	40 (48.2)	.83
Body surface area, m ²	1.65 ± 0.19	1.60 ± 0.18	1.66 ± 0.20	.24
Hypertension, n (%)	53 (46.1)	12 (37.5)	41 (49.4)	.40
Diabetes mellitus, n (%)	23 (20)	6 (18.8)	17 (20.5)	>.99
Echocardiographic data				
LV end-systolic dimension, mm	36.4 ± 11.5	38.5 ± 14.5	35.5 ± 10.2	.26
LV end-diastolic dimension, mm	53.1 ± 9.6	54.2 ± 11.6	52.7 ± 8.8	.48
LV ejection fraction, %	57.1 ± 14.3	51.7 ± 16.7	55.0 ± 13.3	.22
LV mass, g	192.4 ± 73.8	186.4 ± 67.3	194.8 ± 76.4	.54
Operation type				
Valve surgery, n (%)	31 (30.0)	10 (31.3)	21 (25.3)	.49
CABG, n (%)	25 (21.7)	8 (25)	17 (20.5)	
Valve + CABG, n (%)	15 (13.0)	2 (6.3)	13 (15.7)	
Aorta surgery, n (%)	9 (7.8)	2 (6.3)	7 (8.4)	
Aorta + valve or CABG, n (%)	18 (15.7)	3 (9.4)	15 (18.1)	
Others, n (%)	17 (14.8)	7 (21.9)	10 (12.0)	
Previous cardiac surgery, n (%)	14 (12.2)	2 (6.3)	12 (14.5)	.34
ACC time, min	104.7 ± 83.5	109.5 ± 76.3	102.9 ± 86.6	.98
CPB time, min	232.4 ± 134.0	190.0 ± 85.9	248.6 ± 146.1	.014

Values are n (%) or mean ± SD. ACC, Aortic crossclamp; CABG, coronary arterial bypass grafting; CPB, cardiopulmonary bypass; LV, left ventricular.

intracerebral hemorrhage in 1 patient, and gastrointestinal bleeding in 1 patient. Consequently, including 2 heart transplantation recipients, 32 patients (27.8%) survived to discharge.

On logistic regression analysis, a high blood lactate level before ECLS (RR, 1.19; 95% CI, 1.06-1.34) and CPB weaning failure after surgery (RR, 4.39; 95% CI, 1.44-13.35) emerged as significant and independent baseline risk factors of mortality (Table 4).

After adjustment with these baseline risk factors, high blood lactate levels at 6 hours (RR, 1.24; 95% CI, 1.06-1.46), 12 hours (RR, 1.35; 95% CI, 1.10-1.67), and 24 hours (RR, 1.46; 95% CI, 1.10-1.93) after the initiation of ECLS were significantly predictive of mortality (Table 4). The predictive values of serial blood lactate levels after the initiation of ECLS for mortality were assessed using

the ROC method. The greatest accuracy for prediction of mortality was obtained at cutoff values of 7.05 mmol/L at 6 hours (sensitivity, 75.5%; specificity, 75.0%), 4.95 mmol/L at 12 hours (sensitivity, 70.4%; specificity, 76%), and 4.15 mmol/L at 24 hours (sensitivity, 62%; specificity, 93.1%), showing an area under curve of 0.76 at 6 hours, 0.79 at 12 hours, and 0.76 at 24 hours after the initiation of ECLS (Figure 2).

Complications tended to occur less frequently in patients whose lactate level was below the cutoff value than those whose lactate level was greater than the cutoff value at each point (Figure 3).

The differences in survival according to the arterial blood lactate levels after the initiation of ECLS are illustrated in Figure 4. Survivals were higher in the patients whose arterial blood lactate level was below the cutoff values

TABLE 2. Extracorporeal life support data

Variables	Total (n = 115)	Discharged (n = 32)	Died in-hospital (n = 83)	P value
Clinical situation of ECLS implantation				
At the end of operation, n (%)	41 (35.7)	6 (18.8)	35 (42.2)	.029
Arrest, n (%)	27 (23.5)	7 (21.9)	20 (24.1)	.80
Interval from operation finish to ECLS, h	13.5 (0.6-701.9)	11.3 (0.8-50.8)	14.1 (0.6-701.9)	.051
Blood lactate level, mmol/L				
Before initiating ECLS	9.07 ± 4.59	7.33 ± 3.90	9.78 ± 4.67	.002
6 h after ECLS initiation	8.47 ± 4.61	5.81 ± 3.47	9.92 ± 4.54	<.001
12 h after ECLS initiation	6.73 ± 4.54	3.77 ± 2.19	8.16 ± 4.70	<.001
24 h after ECLS initiation	5.27 ± 4.27	2.87 ± 1.28	6.71 ± 4.77	<.001
Duration of ECLS, h	71.3 (0.5-712.9)	70 (0.8-460)	71.9 (0.5-712.9)	.29
Use of nafamostat anticoagulant, n (%)	26 (22.6)	11 (34.4)	15 (18.1)	.12

Values are n (%) mean ± standard deviation or median (range). ECLS, Extracorporeal life support.

TABLE 3. Early outcomes of patients who underwent extracorporeal life support

	Total (n = 115)
In-hospital death, n (%)	83 (72.2)
Successful weaning, n (%)	47 (40.8)
No. of patients with complications during ECLS	
Mediastinal bleeding, n (%)	42 (36.5)
Reoperation for bleeding	31 (27.0)
Massive bleeding (not operated)	11 (9.6)
Lower limb ischemia, n (%)	19 (16.5)
Bowel ischemia, n (%)	8 (7.0)
Cannulation-related complications, n (%)	13 (11.3)

Values are n (%). ECLS, Extracorporeal life support.

than in the patients whose lactate level was greater than cutoff values at each point.

DISCUSSION

Although the establishment of reliable markers to monitor adequate tissue perfusion during ECLS is clinically important to improve outcomes, clinical studies regarding monitoring tools during ECLS have been rare to date. Because reduced arterial pulse pressure is known to be indicative of decreased left ventricular systolic function,⁶

a recent study suggested arterial pulse pressure as a prognostic marker for mortality in patients receiving ECLS.⁷ However, arterial pulse pressure neither reflects the degree of tissue perfusion nor has an indeterminate nature; therefore, its use as a reliable monitoring tool during ECLS is doubtful.

Mixed venous oxygen saturation, a commonly used monitoring parameter in ICU, measured from the pulmonary artery, represents the balance between oxygen delivery and consumption.⁸ A significant proportion of patients receiving ECLS are typically seriously collapsed in hemodynamics at the time of ECLS. Consequently, peripheral arteriovenous shunt and blockade of oxygen delivery frequently appear in those patients. In this situation, mixed venous oxygen saturation is known to be unreliable and inadequate to monitor tissue perfusion. Furthermore, early detection and identification of end-organ injury, and consequences of the tissue hypoxia, are not available.

Pyruvate, intermediate metabolite of glycolysis, is converted to lactate by lactate dehydrogenase in anaerobic condition. The normal plasma lactate level is generally kept at 0.3 to 1.3 mmol/L, which represents a balance between lactate production and removal. However, tissue

FIGURE 1. Flowchart of the outcomes in patients receiving ECLS. ECLS, Extracorporeal life support.

TABLE 4. Multivariable risk factors analyses for in-hospital mortality and impact of lactate level on mortality

Variables	RR	95% CI	P value
Pre-ECLS baseline variables			
Arterial lactate level before ECLS	1.19	1.06-1.34	.003
CPB weaning failure after surgery	4.39	1.44-13.35	.009
Arterial lactate levels during ECLS*			
6 h after ECLS initiation	1.24	1.06-1.46	.009
12 h after ECLS initiation	1.35	1.10-1.67	.005
24 h after ECLS initiation	1.46	1.10-1.93	.008

CI, Confidence interval; CPB, cardiopulmonary bypass; ECLS, extracorporeal life support; RR, relative risk. *Adjusted by “arterial lactate level before ECLS” and “CPB weaning failure.”

hypoxia forces anaerobic metabolism of glucose, which leads to enhanced production of lactate than its removal, resulting in hyperlactatemia. Several studies have shown intimate associations of elevated lactate level with worse outcomes in major cardiac surgery.^{9,10} Increased lactate release during reperfusion after cardioplegic arrest in cardiac surgical patients is known to be an independent predictor of low cardiac output syndrome.³ A recent study by Hajjar and colleagues⁴ demonstrated that the lactate level 6 hours after ICU admission is an independent predictor for major complications after cardiac surgery, and they suggested that a strategy of aiming to lower serum lactate level using other hemodynamic parameters may

reduce the incidence of major complications after cardiac surgery. Furthermore, a prospective, randomized study demonstrated that normalization of lactate level as a therapeutic goal can shorten the length of hospital day and decrease the morbidity.¹¹

Consistent with the cited reports, our previous study showed a close association between high blood lactate level and mortality in patients who underwent ECLS after major cardiac surgery.⁵ High lactate level before ECLS initiation was an independent predictor of mortality, and the lactate level of 7.9 mmol/L before initiation of ECLS, assessed using the ROC method, was the most accurate predictive value for mortality. This result is supported by other studies.^{12,13}

ECLS can provide total circulatory support with fully oxygenated blood so that oxygen delivery and systemic tissue perfusion are satisfied in patients with severe respiratory or circulatory failure. Consequent rapid decrement of lactate level is expected in these patients. Nevertheless, a significant number of patients who underwent ECLS do not seem to show a remarkable decrement in blood lactate level. We hypothesized that the patients who do not show an appropriate decrement in blood lactate level after the initiation of ECLS may have inadequate tissue perfusion related to complications or insufficient support. The present study demonstrated that serially measured arterial blood lactate levels at 6 hours,

FIGURE 2. ROC curves for the predictive value of arterial lactate level for mortality at 6 hours (A), 12 hours (B), and 24 hours (C) after the initiation of ECLS. AUC, Area under the curve; CI, confidence interval.

FIGURE 3. The incidence rate of the overall complications according to the cutoff arterial lactate levels at 6 hours, 12 hours, and 24 hours after the initiation of ECLS. ECLS, Extracorporeal life support.

12 hours, and 24 hours after ECLS initiation were independent predictors of mortality even after adjustment with pre-ECLS risk factors. The cutoff values of predictive

for mortality gradually declined in serially measured lactate level after ECLS initiation (Figure 2). These findings suggest that the failure to achieve adequate decrement in arterial lactate level shortly after ECLS initiation is associated with increased mortality in patients with hyperlactatemia. Therefore, in patients without an adequate decrement in lactate levels during ECLS, potential factors responsible for inadequate perfusion should be identified and corrected. In these regards, this study proposes arterial lactate measurement as a monitoring tool during ECLS for the acquisition of satisfactory tissue perfusion. Although previous studies also have demonstrated an association between the high blood lactate level after initiation of ECLS and mortality or weaning failure,¹⁴⁻¹⁶ the cited studies have not shown the predictive role of lactate measurement as a monitoring tool during ECLS.

Chen and colleagues¹⁵ showed a significant correlation between survival and lactate levels on the first, third, and seventh days of ECLS. Another recent study also demonstrated that patients who survived to discharge showed significantly lower levels of lactate at 48 and 72 hours than nonsurvivors.¹⁴ Compared with these earlier studies, the present study evaluated the influences of blood

FIGURE 4. Kaplan–Meier analysis revealing differences in mortality according to the arterial lactate level at 6 hours (A), 12 hours (B), and 24 hours (C) after the initiation of ECLS. Lac, Lactate.

lactate levels focusing more on the very early period (within 24 hours). This is because the postoperative courses of patients who underwent major cardiac surgery are dynamic, especially in those who require ECLS, in that patients' outcomes are likely to be determined in the very early postoperative period. For instance, of 83 patients who died in-hospital in the present study, 23 (27.7%) died within 3 days of ECLS support and 47 (56.6%) died within 7 days. These findings indicate that referencing the lactate levels at 3 or 7 days is too late for many patients; therefore, we need to establish more reasonable monitoring methods for very early settings. This is why we focused on the relatively earlier period of the course compared with other previous studies.

New techniques, such as laser-Doppler flowmetry, near-infrared spectroscopy, and sidestream dark-field imaging, have been introduced to evaluate tissue perfusion and microcirculation at the bedside.¹⁷⁻¹⁹ Although these techniques might be used as a tailored therapy in the foreseeable future, practical application of these equipment and techniques during ECLS in a routine way may not be feasible because of the associated costs.

Study Limitations

This study is subject to the limitations inherent in retrospective studies of observational data from a single center. The study failed to elucidate the direct relation between the elevated lactate level after the initiation of ECLS and each complication during ECLS, such as hemorrhage, bowel ischemia, cannulation-related, and device-related complications. This may account for the relatively small number of patients who experienced each complication.

Lactate level-guided intervention during ECLS is an important issue according to the study results. However, the present study could not evaluate whether lactate level-guided intervention decreased mortality. To address this issue, "intention-to-treat" basis analyses should be performed, which is only possible through studies with prospective designs.

CONCLUSIONS

Establishment of reliable markers to monitor adequate tissue perfusion during ECLS is clinically important to improve outcomes. Arterial lactate level after the initiation of ECLS is strongly predictive of mortality and has the tendency to decrease sequentially in patients acquiring satisfactory tissue perfusion. Therefore, arterial lactate measurement can be used as a valuable and reliable tool for monitoring adequate tissue perfusion during ECLS. In patients without adequate decrement in lactate levels during ECLS, potential factors responsible for inadequate

perfusion should be identified and corrected. Prospective, randomized studies targeting normalization of the lactate level as a therapeutic goal are required to verify the impact of post-ECLS arterial lactate measurement on the outcomes of ECLS.

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