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Original Articles

Is There an Association between Hyperglycemia and Clinical Outcome in Adult Patients Receiving Extracorporeal Membrane Oxygenation

Song Lou, MD; Jingwen Li, MD; Cun Long, MD; Feilong Hei, MD; Kun Yu, MD; Shigang Wang, MD

Department of Cardiopulmonary Bypass, Cardiovascular Institute and FuWai Hospital, California MS and PUMC, Beijing, China

Abstract: Perioperative hyperglycemia frequently develops in critically ill patients and has been associated with adverse outcome. In this study, we tried to identify whether hyperglycemia was associated with adverse outcome in adult patients receiving extracorporeal membrane oxygenation. From 2004 through 2008, 44 adult patients received extracorporeal membrane oxygenation. Clinical records of these 44 consecutive patients were retrospectively analyzed. Glucose levels were monitored and recorded every 3 hours during the support period. The mean glucose level was computed for all patients for whom data were available within the first 48 hours after extracorporeal membrane oxygenation setup. More than 15% of blood glucose levels above 180 mg/dL were defined as hyperglycemia. Clinical outcomes were compared between patients with and without hyperglycemia. The primary outcome was death from any cause in hospital. A p value < .05 was accepted as significant. The overall survival was 68%. Twenty-eight patients were allocated to group 1 with a mean glucose of 179 ± 40 mg per deciliter. The other 16 patients allocated to group 2 with a mean glucose of 140 ± 16 mg per deciliter. There is no significant difference in the mortality of the two groups. Perioperative complications were also similar between the two groups. Glucose levels were not associated with mortality and complications in adult patients receiving extracorporeal membrane oxygenation.
Keywords: adult, extracorporeal membrane oxygenation, mortality, glucose level. *JECT. 2010;42:281–285*

Perioperative hyperglycemia frequently develops in critically ill patients and has been associated with adverse outcome. Carbohydrate metabolism is regulated by insulin, glucagon, cortisol, growth hormone, and epinephrine, the concentrations of which are often perturbed in critical care patients, especially those undergoing cardiac surgery with cardiopulmonary bypass. A high glucose level during cardiopulmonary bypass was an independent predictor of mortality and major adverse events in both diabetic and nondiabetic patients (1). Patients with blood glucose values >200 mg per deciliter immediately after coronary artery bypass grafting (CABG) had an increased risk of mortality and postoperative complications (2).

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Address correspondence to: Cun Long, MD, Department of Cardiopulmonary Bypass, Cardiovascular Institute and Fu Wai Hospital, CAMS and PUMC, 167 Beilishilu Beijing 100037, China. E-mail: fuwaicpb@mx.cei.gov.cn
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In 2001 Van Den Berghe (3) published a randomized controlled trial of critically ill surgical patients showing that intensive insulin therapy to maintain blood glucose at or below 110 mg per deciliter reduces mortality among critically ill patients in the surgical intensive care unit by one third. The results of this trial were enthusiastically received and rapidly incorporated into guidelines, which have led to worldwide adoption of tight glucose control in critically ill patients. Tight glucose control for patients treated in intensive care units (ICUs) has been recommended by many professional organizations (4). Different methods assessing the quality of glucose control have been developed (5).

It is reported that at least 1% of all patients who have undergone cardiac procedures require mechanical devices to support the failing heart (6,7). Extracorporeal membrane oxygenation (ECMO) is still the first option for short-term cardiac support while waiting for either native heart recovery or as a bridge to transplantation. ECMO usage raises hospital costs and resource consumption, with high short-term mortality (6–9). Every attempt should be made to improve the outcome of these patients.

From January 2004 through December 2008, 44 adult patients in our institution received ECMO support and their plasma glucose levels were recorded. In this study, we retrospectively reviewed the medical records of these patients. Our purpose is to determine if glucose levels are associated with clinical outcomes.

MATERIALS AND METHODS

The ECMO program was started in our institution in January 2004. Since then and until December 2008, 21,298 adult patients underwent cardiac operations, 44 patients (.2%) received ECMO for primary or postcardiotomy cardiogenic shock. We retrospectively analyzed the medical records of these 44 patients and evaluated the association between hyperglycemia and clinical outcomes. Our institutional review board approved the study with waiver of informed consent because this observational study did not modify existing diagnostic or therapeutic strategies and did not contain any identifiable private information.

ECMO support was initiated under the following circumstances: failure of weaning from cardiopulmonary bypass (CPB) and postoperative low cardiac output unresponsive to conventional therapies. Exclusion criteria for ECMO support in our institution were the following: mechanical ventilation for at least 7 days, irreversible neurologic dysfunction, and contraindication to anticoagulation and uncorrected cardiac anomalies.

The circuit was primed with multiple electrolyte injections without plasma expanders. ECMO system was installed in ICU or operating room. Intra-aortic balloon counterpulsation (IABP) was used in eight patients (18.2%) prior to the ECMO setup with the aim of reducing the after load to improve the coronary perfusion and maintaining a pulsatile flow. A bolus of heparin (100 units/kg) was given intravenously before cannulation. If cannulation was not performed within 30 minutes, activated clotting time (ACT) was measured again.

The ECMO blood flow was adjusted to achieve a mixed venous oxygen saturation of 65%–70%. Fraction of inspired oxygen was titrated to maintain a post oxygenator partial oxygen pressure of 300 mmHg or greater. Carbon dioxide was kept within the normal range by adjusting the sweep flow.

Continuous heparin infusion with an initial rate of 4 U/kg/min was started when active hemorrhage had been controlled. Intravenous heparin infusion was titrated to achieve an activated clotting time of 140–200 seconds, depending on clinical judgment for the risk of bleeding. Platelets were administered to maintain a platelet count more than 50×10^9/L. Other blood products such as packed red blood cells and fresh frozen plasma were infused as required.

All the patients were ventilated by intermittent mandatory ventilation mode of 10/min. Ventilator setting was commonly set at a tidal volume of 8–12 mL/kg, positive end expiration pressure of 6–8 mmHg, and inspired oxygen fraction of 40%. A peak airway pressure >35 cmH2O was avoided. While on ECMO, ventilation settings are adjusted according to the flow rate to fully provide the gas exchange and oxygenation. Inotropic agents were reduced to a minimum level to allow for optimal myocardial recovery. In patients with a motionless left ventricle, small doses of inotropes were given to obtain a minimal ventricular contraction to avoid thrombosis inside the left ventricle. Bedside heart examinations by trans-thoracic echo were performed daily to assess the left ventricle motion.

The circuit was checked daily and changed when significant fibrin deposition or clots accumulated on the membrane, hemolysis or thrombocythemia, or incapacity of blood oxygenation. We preferred to replace the entire ECMO system for safety and simplicity. Eight patients experienced circuit change.

Weaning was considered when oxygenation improved and less support was required. Step-by-step weaning was the main strategy. The ECMO flow rate was lowered progressively over a period of several hours. Patients were weaned to 10% of their calculated cardiac output, and then were taken off ECMO. ACT between 180 and 200 seconds was obtained during weaning attempts. When ECMO weaning was impossible, bridging to transplantation was considered. ECMO had to be withdrawn from some patients, at the family members' request, with the knowledge that survival was unlikely and continued support was futile.

Insulin was administered if the blood glucose level exceeded 200 mg per deciliter at the discretion of the treating clinicians. Insulin control of blood glucose was achieved with the use of an intravenous infusion of insulin in saline or subcutaneous injection.

Blood samples for glucose measurement were obtained by means of arterial catheters. All these patients' glucose levels were monitored and recorded every 3 hours during the support period. The mean glucose levels were computed for all patients for whom data were available within the first 48 hours after ECMO setup. More than 15% of blood glucose levels above 180 mg/dL were defined as hyperglycemia. The primary outcome was death from any cause in hospital. Secondary outcome were ECMO related complications including re-exploration for bleeding, blood culture proven infection, renal failure (serum creatinine > 132 umol/L and requiring dialysis), hepatic dysfunction (alanine aminotransferase > 500 IU/L or aspartate aminotransferase > 500 IU/L), neurological dysfunction (confusion, documented focal or overall deficit), or multiple organ dysfunction.

All statistical evaluations were performed with the SPSS software (version 16.0 for Windows; SPSS Inc., Chicago, IL).

Continuous variables were expressed as mean with one standard deviation or standard error and were compared with Student's *t* test or the Mann-Whitney *U* test, as appropriate. Categorical variables were expressed as percentages and were evaluated with the Fisher's exact test or the chi-square test. A p value < .05 was accepted as significant.

RESULTS

From January 2004 through December 2008, 44 adult patients with postcardiotomy shock were put on ECMO in our institution. Mean age of the patients was 50.0 ± 14.2 years and mean body weight was 65.5 ± 11.3 kg. Thirty-four patients were male.

Of the 44 patients, 14 patients received CABG, 10 patients received valve replacement or valvuloplasty, two patients received combined CABG and valve replacement, four patients received congenital heart disease correction, eight patients received heart transplantation, and six patients received other procedures. Other procedures included: one patient received combined CABG and great vessels procedure, two patients received pericardial stripping, two patients received pulmonary thromboendarterectomy, and another one patient received Bentall procedure. Nine percent of the procedures were redo operations.

Cardiopulmonary resuscitation (CPR) was applied in 13 patients (30%) with a mean duration of 31 ± 22 minutes. Eight (18%) patients had received an IABP before ECMO implantation. The indication of ECMO setup was failure of weaning from CPB in 22 patients (50%) and low cardiac output in 22 patients (50%). The ECMO was established in the operation room in 24 patients (55%) or in the ICU in 20 patients (45%). Mean plasma lactate level prior to ECMO establishment was 11.0 ± 6.0 mmol/L.

Mean ECMO duration was 116 ± 70 hours. Of the 33 patients who were weaned from ECMO, 30 were subsequently discharged from the hospital. The other three patients died from low cardiac output syndrome, pulmonary failure, and renal failure.

Thirty-three patients experienced at least one major ECMO related complication. Each patient had 2.0 ± 2.0 complications on average. ECMO related complications are summarized in Table 1.

Twenty-eight patients experienced hyperglycemia with a mean glucose of 179 ± 40 mg per deciliter. The other 16 patients had a mean glucose of 146 ± 16 mg per deciliter. Pre-ECMO data are comparable between the two groups (Table 2). Eight patients with hyperglycemia and six patients without hyperglycemia died before discharge. There is no significant difference in the mortality of the two groups (8/28 vs 6/16 p = .541). ECMO related complications were also similar between the two groups (Table 3).

Table 1. ECMO related complications.

ECMO Related Complications	Incidence (percentage)
Re-exploration for bleeding	16/44 (36%)
Blood culture proven infection	4/44 (9%)
Renal failure (serum creatinine > 132 umol/L and requiring dialysis)	8/44 (18%)
Hepatic dysfunction (ALT > 500 IU/L or AST > 500 IU/L)	4/44 (9%)
Neurological dysfunction (confusion, documented focal, or overall deficit)	2/44 (5%)
Multiple organ dysfunction	2/44 (5%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; TBIL, total bilirubin.

Table 2. Comparison of pre-ECMO characters between groups.

	Hyperglycemia	Non-Hyperglycemia	*p*
Gender (male/female)	22/6	12/4	1.000
Age (years)	49.4 ± 14.6	51.0 ± 13.9	.717
Weight (Kg)	64.9 ± 10.9	66.4 ± 12.2	.669
Pre-ECMO CPR (y/n)	10/18	3/13	.314
Pre-ECMO IABP (y/n)	6/22	2/14	.689
ECMO setup location (OR/ICU)	15/13	9/7	.864
Pre-ECMO lactate (mmol/L)	12.1 ± 6.0	9.2 ± 5.8	.136
Indication			.210
LCOS	16	6	
Failure of weaning from CPB	12	10	
Procedure			.316
CABG	11	3	
Valvular operation	5	5	
CBAB + valvular operation	2	0	
Congenital heart disease correction	3	1	
Heart transplantation	5	3	
Other procedures	2	4	

LCOS, Low Cardiac Output Syndrome; OR, Operation Room; CABG, coronary artery bypass graft.

Table 3. Comparison of ECMO related complications between groups.

	Hyperglycemia	Non-Hyperglycemia	*p*
Any complication (y/n)	19/9	12/4	.738
Re-exploration (y/n)	13/15	3/13	.066
Infection (y/n)	3/25	1/15	1.000
Renal failure (y/n)	3/25	5/11	.117
Hepatic dysfunction (y/n)	3/25	5/11	.117
Neurologic dysfunction (y/n)	1/27	1/15	1.000
MODS (y/n)	0/28	2/14	.127

MODS, Multiple Organs Dysfunction Syndrome.

DISCUSSION

Hyperglycemia accompanies critical illness and the severity of this diabetes of stress is considered a risk factor of death. Since Van Den Berghe demonstrated the benefit of tight glucose control in critically ill surgical patients (3),

more attention has been paid to intensive insulin therapy and its effect on clinical outcome. Ingels et al. (10) showed that survival benefit obtained with insulin-titrated glucose control during intensive care after cardiac surgery was maintained after 4 years, without inducing increased medical care requirements. Van Den Berghe (11) later in 2006 also suggested that intensive insulin therapy significantly reduced morbidity and mortality in medical ICU patients especially those treated for 3 or more days.

The Society of Thoracic Surgeons recommended glycemic control (<180 mg per deciliter) in adult patients with or without diabetes during and immediately after cardiac surgery (4). Also, achieving 85% of blood glucose levels within optimal range may be considered gold standard in glucose control (5). We tried to demonstrate whether the recommendation could be applied to adult patients receiving ECMO after cardiac surgery who had higher risk of mortality. Therefore, in the present study we defined hyperglycemia as more than 15% blood glucose levels obtained above 180 mg per deciliter.

Although tight glucose control for patients treated in ICUs has been recommended by many professional organizations, conflicting results were obtained from subsequent randomized controlled trials of tight glucose control in ICU settings. Arabi et al. (12) indicated that intensive insulin therapy was not associated with improved survival among medical surgical intensive care unit patients and was associated with increased occurrence of hypoglycemia, which was related to risk of death in some studies (13). In a recent study involving 6014 critically ill patients, tight glucose control was associated with hypoglycemia and increased mortality at 90 days. The authors did not recommend use of the lower target (81–110 mg per deciliter) in critically ill patients (14). A meta-analysis by Wiener et al. (15) showed that in critically ill adult patients, tight glucose control is not associated with significantly reduced hospital mortality but is associated with an increased risk of hypoglycemia. Sensitivity analysis suggests this is true whether the level of glucose control is <150 or <110 mg per deciliter and independent of the type of ICU (medical, surgical, or combined) (15). Hence, the risks and benefits of tight glucose control must therefore be carefully weighed for each subgroup of ICU patients before any modification to the current therapy strategy is adopted. From the data available, it may not be necessary to obtain a glucose level ≤180 mg per deciliter at the expense of increased hypoglycemia, which is fatal sometimes. We could not exclude the possibility that intensive glucose control may benefit some patients. It may be more important to evaluate the role of tight glucose control in specific populations.

ECMO is a justifiable alternative treatment for postoperative refractory cardiac dysfunction, which could rescue more than 60 percent of selected patients. The high mortality and high cost of ECMO therapy make it necessary to make every attempt to improve the outcome of these patients. To the best of the author's knowledge, this is the first study to evaluate the association between glucose level and clinical outcomes in adult patients receiving ECMO support. At present, many investigations regarding patients on ECMO are observational. One of the possible reasons is that it will be more difficult and sometimes unethical to perform a randomized, controlled trial in this special group of dying patients. An observational study may be the first step in resolving the important and still unanswered question, whether patients on ECMO would benefit from tight glucose control.

In this study, we divided the patients into two groups according to the obtained glucose level during ECMO therapy instead of the target glucose level. This may better reflect the carbohydrate metabolism profile of the patients. We considered a reduction in hospital mortality to be the most important potential benefit of tight glucose control. Hospital mortality was defined as death that occurred during the hospital stay. Some factors have been identified as predictors of mortality or survival, including receiving CPR before ECMO initiation (9) and age (6). That all the above factors are comparable between the two groups suggested that the potential confounding factors were well balanced. Although CPR has been identified as a risk factor for mortality (9), it was not associated with in-hospital mortality in the present study. Of the 44 patients, 13 received CPR before ECMO setup. In this group, eight died before discharge. The mortality is 62%, which is not significantly different from that of patients not receiving CPR. There was not a difference of mean glucose level in those that had CPR and those that did not (170 ± 39 mg/dL vs 163 ± 38 mg/dL).

Some limitations should be acknowledged and the results of our study must be interpreted cautiously for several reasons. First, it was a single center, observational study. Causality could not be developed from our data. Second, that follow-up information was not provided makes long term survival analysis and quality-of-life evaluation impossible. Third, that intensive insulin therapy was not adopted and few episodes of hypoglycemia were reported in our series made the evaluation of hypoglycemia and outcome impossible. In fact, there is no interventional difference between the two groups. The fact that the glucose levels of the two groups were different could be attributed, in part, to the following factors (1). Patients not exhibiting hyperglycemia during ECMO support might have an impaired ability to mount an appropriate stress response. Whether this impaired stress response adversely affects the outcome is unknown (2). Some potential confounding variables such as exogenous catecholamine administration and nutritional strategies were believed to influence the glucose level during ECMO support. Another important limitation is that we could not account for differences in

such confounding variables during the study period as carbohydrate administration, including glucose infusion from maintenance fluids, or enteral feeds and exogenous catecholamine administration. Finally, the sample size is pretty limited. We used the power calculation for two proportions with unequal sample size to calculate the power of the test of mortality between the two groups. The power is only about 10%. There is the possibility that there is real difference in mortality between the groups, which could not be detected by our sample. Therefore, further study with larger sample size is warranted.

CONCLUSION

Given the findings of our study, it seems appropriate that tight glucose control in patients undergoing ECMO should be reevaluated until the results of larger, more definitive clinical trials are available.

REFERENCES

1. Doenst T, Wijeysundera D, Karkouti K, et al. Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. J Thorac Cardiovasc Surg. 2005;130:1144.
2. Jones KW, Cain AS, Mitchell JH, et al. Hyperglycemia predicts mortality after CABG: Postoperative hyperglycemia predicts dramatic increases in mortality after coronary artery bypass graft surgery. J Diabetes Complications. 2008;22:365–70.
3. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345:1359–67.
4. Lazar HL, McDonnell M, Chipkin SR, et al. The Society of Thoracic Surgeons Practice Guideline Series: Blood glucose management during adult cardiac surgery. Ann Thorac Surg. 2009;87:663–9.
5. Goldberg PA, Bozzo JE, Thomas PG, et al. "Glucometrics"—assessing the quality of inpatient glucose management. Diabetes Technol Ther. 2006;8:560–9.
6. Doll N, Kiaii B, Borger M, et al. Five-year results of 219 consecutive patients treated with extracorporeal membrane oxygenation for refractory postoperative cardiogenic shock. Ann Thorac Surg. 2004;77:151–7.
7. Ko WJ, Lin CY, Chen RJ, Wang SS, Lin FY, Chen YS. Extracorporeal membrane oxygenation support for adult postcardiotomy cardiogenic shock. Ann Thorac Surg. 2002;73:538–45.
8. Zhang R, Kofidis T, Kamiya H, et al. Creatine kinase isoenzyme MB relative index as predictor of mortality on extracorporeal membrane oxygenation support for postcardiotomy cardiogenic shock in adult patients. Eur J Cardiothorac Surg. 2006;30:617–20.
9. Combes A, Leprince P, Luyt CE, et al. Outcomes and long-term quality-of-life of patients supported by extracorporeal membrane oxygenation for refractory cardiogenic shock. Crit Care Med. 2008;36: 1404–11.
10. Ingels C, Debaveye Y, Milants I, et al. Strict blood glucose control with insulin during intensive care after cardiac surgery: Impact on 4-years survival, dependency on medical care, and quality-of-life. Eur Heart J. 2006;27:2716–24.
11. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354:449–61.
12. Arabi YM, Dabbagh OC, Tamim HM, Al-Shimemeri AA, Memish ZA, Haddad SH. Intensive versus conventional insulin therapy: A randomized controlled trial in medical and surgical critically ill patients. Crit Care Med. 2008;36:3190–7.
13. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008; 358:125–39.
14. NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360: 1283–97.
15. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: A meta-analysis. JAMA. 2008;300: 933–44.