The Incidence, Risk Factors, and Outcomes of Hyperlactatemia after Heart Transplantation

One Center's Experience

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Summary

Hyperlactatemia (HL) is associated with tissue hypoperfusion during cardiac surgery, which results in post-operative morbidity and mortality among patients undergoing cardiopulmonary bypass surgery. The aim of this study was to determine the incidence, risk factors, and outcome of HL after heart transplantation (HTx) in one of the largest Japanese single-center cohorts. We retrospectively studied the lactate levels in 49 patients who underwent HTx at the University of Tokyo Hospital from August 1, 2010 to November 30, 2015. All of the patients were over 20 years of age. Arterial blood samples were analyzed during the operation and until 24 hours after surgery. Twenty-nine patients (59.2%) had HL after intensive-care unit admission. At 24 hours after surgery, the lactate levels of all patients had recovered to the normal range. A multivariate analysis showed that the total ischemic time of the donor heart (odds ratio [OR], 1.0176; 95% confidence interval [CI], 1.0004-1.0375; $P = 0.0444$) and the duration of preoperative left ventricular assist device (LVAD) support (OR, 0.9977; 95% CI, 0.9952-0.9997; $P = 0.0218$) were risk factors for HL. Pulmonary complications were noted in 24.1% of the patients with high lactate values but in none of the patients without HL ($P = 0.0182$); however, there were no cases of hospital death, and the length of hospital stay did not differ to a statistically significant degree between HL groups ($P = 0.719$). Although HL after HTx was common, it appeared to be transient and benign. Donor heart ischemia and the duration of preoperative LVAD support were associated with HL after transplantation.

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Key words: Donor heart ischemia

Lactic acidosis is related to tissue hypoperfusion and hypoxia in critically ill patients with sepsis⁽¹⁾ or after cardiogenic shock⁽²⁻⁴⁾ and is associated with a poor prognosis when left untreated. Under anaerobic conditions, cellular metabolism converts pyruvate to lactate. The lactic acid levels, which are related to the oxygen debt, correspond to the severity of tissue hypoperfusion, and lactic acidosis or hyperlactatemia (HL) is a well-recognized marker of circulatory failure.

HL is a common phenomenon, especially during and after cardiac surgery with cardiopulmonary bypass (CPB),⁽⁵⁾ and is associated with postoperative morbidity and mortality.⁽⁶⁾ Several mechanisms have been proposed to explain its pathogenesis. Some reports suggest that the degree of hemodilution and low peripheral oxygen delivery leads to tissue hypoxia.^(7,8) Similarly, splanchnic and renal hypoperfusion are likely to lead to a reduced lactate clearance. A relationship has been suggested between lactic acidosis and the reduction of the preoperative afterload by angiotensin-converting enzyme inhibitors (ACEIs) or other drugs that are administered preoperatively to treat heart failure.⁽⁹⁾

No reports have so far described the incidence, risk

factors, or outcomes of HL after HTx in Japan. The aims of the present study were to assess the prognostic significance of HL and to determine the incidence and risk factors for HL after HTx in one of the largest Japanese single-center cohorts.

Methods

Study patients: The study included 54 consecutive patients who had undergone HTx at the University of Tokyo Hospital between August 2011 and November 2015. After excluding five patients who were younger than 20 years of age, a total of 49 patients were included in the analysis. This study complied with the Declaration of Helsinki, and written informed consent was obtained from each patient regarding the use of his or her clinical data.

The patients were divided into two groups based on the peak lactate level within 24 hours after HTx. The HL group included patients whose peak lactate level was ≥ 4 mmol/L; all other patients were classified into the nonhyperlactatemia (NHL) group. We set 4 mmol/L as the cut-off level based on the threshold of early goal-directed therapy in the treatment of severe sepsis and septic

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shock.¹⁰⁾

HTx procedures: All donor hearts were examined by echocardiography and explanted from suitable donors. During organ procurement, the donor hearts were arrested and preserved with Celsior solution (Pasteur Merieux, Paris, France). The total ischemic time was 254.3 ± 38.3 minutes. The anesthesia techniques and medications were similar for all patients. Anesthesia was induced and maintained using a combination of propofol, fentanyl, or midazolam and a neuromuscular paralytic agent. Most patients received an inhaled anesthetic (sevoflurane). Standard median sternotomy and aorta/bicaval cannulation were performed for CPB. The pump circuit was primed with lactate Ringer solution (L-lactate: 11.2-19.6 mEq). The rectal temperature was cooled to 28°C. The nonpulsatile blood flow was adjusted to maintain a blood flow of approximately 2.6-2.7 l/minute/m². Red blood cell transfusion was performed as necessary to maintain a hematocrit level of approximately 23%-24%. All patients were retransfused with lost blood (Cell Saver; Haemonetics Corporation, Braintree, MA, USA). Vaporized isoflurane, nitroglycerin, phenylephrine hydrochloride, or norepinephrine was continuously infused to maintain a perfusion pressure of approximately 50-70 mmHg. Following standard rewarming and de-airing, the pump was discontinued with routine inotropic support, including dopamine at 2-8 µg/kg/minute and low-dose phosphodiesterase III inhibitor treatment to obtain an acceptable cardiac output and isoproterenol or temporary pacing to achieve a heart rate of approximately 90-100 beats/minute. If necessary, dobutamine, epinephrine, and/or norepinephrine infusion was started. In patients with an unstable cardiopulmonary condition, an intra-aortic balloon pump (IABP, $n = 4$) was used or extracorporeal membrane oxygenation (ECMO, $n = 2$) was performed. All patients were sent to the intensive-care unit (ICU) postoperatively with endotracheal intubation. Our standard immunosuppressive regimen includes calcineurin inhibitor, mycophenolate mofetil, and high-dose methylprednisolone.

The lactate level was measured when entering the ICU and thereafter every 6 hours until 24 hours after the operation, and it was additionally measured according to the ICU physician's policy using an ABL 800 FLEX device (RADIOMETER; Copenhagen, Denmark). The lactate (detectable limit, 0.0-30 mmol/L) and glucose (detectable limit, 0-1,081 mg/dl) levels were measured.

Major neurological complications were defined as seizure, stroke, severe diffuse encephalopathy, or severe delirium. Pulmonary complications were defined as mechanical ventilation for > 72 hours. Renal complications were defined as elevated postoperative creatinine levels of > 2.5 mg/dL or the need for hemodialysis or hemofiltration. Graft dysfunction on the first echocardiogram after transplantation was defined as an ejection fraction < 45%. Mortality was defined as hospital mortality.

Statistical analyses: All of the data were expressed as the mean $\pm$ standard deviation or as a percentage. The differences between the two groups were assessed with either Fisher's exact test or a *t*-test, as appropriate. Two-sided *P* values of < 0.05 were considered to indicate statistical significance. A univariate analysis on the risk of HL after

HTx was performed on 43 factors before, during, and after surgery. With respect to factors whose *P* value was < 0.05 among univariate analyzed 43 factors, correlation coefficients and their *P* values were calculated for all combinations in consideration of multicollinearity among factors. When correlation was observed, one factor was excluded from factors of multivariate analysis. Finally, the factors with no correlation were adopted for a multivariate logistic regression model. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The statistical analyses were performed using the JMP[®] Pro software program (version 11.2.0; SAS Institute; Cary, NC, USA).

Results

The patients' characteristics are shown in Table I. HL was observed in 29 of the 49 (59.2%) patients. The mean lactate peak value was 5.9 ± 3.5 mmol/L, and the time to peak lactate was 3.1 ± 3.7 hours. The average age was 42.4 ± 11.6 years, 71.4% of patients were men, and the etiology of heart failure was dilated cardiomyopathy in 65.3% of the patients. With the exception of the duration of preoperative left ventricular assist device (LVAD) support, the two groups had similar preoperative characteristics. The duration of LVAD support was shorter among the patients in the postoperative HL group than in the NHL group (791.0 ± 315.0 versus 1038.8 ± 360.0 , $P = 0.0149$). None of the patients used insulin before surgery. None of the patients had renal or liver dysfunction. The use of ACEIs did not differ markedly between the two groups. The preoperative LVAD flow conditions (continuous or pulsatile) did not differ significantly between the two groups.

The operative data are shown in Table II. The duration of surgery, duration of CPB, amount of blood loss and blood transfusion, maximum dose of catecholamine, and the mean CPB flow did not differ markedly between the two groups. The total ischemic time of the donor heart in the HL group was longer than that in the NHL group (264.6 ± 36.2 versus 239.4 ± 37.1 , $P = 0.0218$).

The postoperative data are shown in Table III. Cardiopulmonary instability, including the need for mechanical support, did not differ markedly between the two groups. The postoperative peak blood glucose and the glucose at the time of peak lactate level (GPL) were significantly higher in the HL group than in the NHL group ($P = 0.0425$, $P = 0.0053$). There were no significant differences between the two groups with regard to the amount of insulin used during the first 24 hours in the ICU.

A univariate analysis of the risk of HL after HTx was performed on 43 factors before, during, and after surgery, and three factors had *P* values < 0.05 (postoperative GPL, duration of preoperative LVAD support, and total ischemic time of the donor heart; $P = 0.0030$, 0.0119, 0.0193, respectively). The correlation coefficients and the levels of significance were calculated for all combinations (Table IV). A correlation was found between the postoperative GPL and the total ischemic time of the donor heart. Because the total ischemic time of the donor heart is fixed during a procedure and the postoperative GPL is measured postoperatively, the temporal context was clear

Table I. The Preoperative Characteristics

Variable	NHL (<i>n</i> = 20)	HL (<i>n</i> = 29)	<i>P</i>
Age, years	42.6 ± 2.6	42.3 ± 2.2	0.9245
Male gender, <i>n</i> (%)	13 (65)	22 (75.9)	0.5237
Body mass index	21.1 ± 2.9	20.4 ± 3.5	0.4533
Left ventricular ejection fraction, %	28.0 ± 18.2	23.0 ± 13.8	0.2852
Pre-transplant etiology			
Idiopathic dilated CM (<i>n</i> = 32), <i>n</i> (%)	12 (60)	20 (69.0)	0.5548
Ischemic CM (<i>n</i> = 7), <i>n</i> (%)	6 (30)	1 (3.4)	
Dilated hypertrophic CM (<i>n</i> = 6), <i>n</i> (%)	1 (5)	5 (17.2)	
Other (<i>n</i> = 4)			
Pretransplant LVAD support duration, days (<i>n</i> = 48)	1038.8 ± 360.0	791.0 ± 315.2	0.0149
CF-LVAD, <i>n</i> (%)	10 (50)	21 (72.4)	0.1388
Hct, %	34.8 ± 6.7	36.4 ± 6.6	0.4116
Total bilirubin, mg/dL	1.0 ± 0.4	0.9 ± 0.4	0.4047
AST, IU/mL	31.6 ± 14.3	35.0 ± 18.3	0.4938
ALT, IU/mL	16.3 ± 7.8	22.8 ± 20.1	0.1770
Creatinin, mg/dL	1.0 ± 0.3	1.0 ± 0.3	0.9993
ACEI use, <i>n</i> (%)	10 (50)	14 (48.3)	1.0

LVAD indicates left ventricular assist device support; CF-LVAD, continuous flow LVAD; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Hct, hematocrit; ACEI, angiotensin-converting enzyme inhibitor; and CM, cardiomyopathy.

Table II. The Operative Data

Variable	NHL (<i>n</i> = 20)	HL (<i>n</i> = 29)	<i>P</i>
Donor heart characteristics			
Total ischemic time of the donor heart, minutes	239.4 ± 37.1	264.6 ± 36.2	0.0218
Age, years	45.8 ± 13.8	45.4 ± 12.1	0.9180
Male gender, <i>n</i> (%)	11 (55)	15 (52)	1.0000
LVEF, %	64.5 ± 8.6	64.2 ± 7.3	0.9045
History of CPR, <i>n</i> (%)	7 (35)	15 (52)	0.3812
Dopamine dose, µg/kg/minute	4.9 ± 6.0	4.4 ± 4.2	0.7738
Noradrenaline dose, µg/kg/minute	0.05 ± 0.2	0.02 ± 0.05	0.3216
Cause of brain death (cerebrovascular accident or not), <i>n</i> (%)	14 (70)	23 (79)	0.5123
Surgery duration, minutes	586.1 ± 23.5	609.9 ± 19.5	0.4397
CPB duration, minutes	179.1 ± 41.2	193.8 ± 59.5	0.3435
Blood loss, mL	4663.8 ± 2000.5	4400.7 ± 2964.8	0.7311
Dopamine, µg/kg/minute	6.8 ± 2.0	6.3 ± 2.1	0.3850
Dobutamine, µg/kg/minute	6.9 ± 2.0	6.1 ± 2.1	0.1821
Epinephrine, µg/kg/minute	0.073 ± 0.15	0.057 ± 0.13	0.6910
Norepinephrine, µg/kg/minute	0.06 ± 0.06	0.14 ± 0.28	0.2329
Red blood cell, units	16.5 ± 7.2	17.9 ± 10.9	0.6054
Fresh-frozen plasma, units	17.9 ± 7.4	20.8 ± 12.3	0.3596
Platelet concentrate, units	34.5 ± 14.3	33.8 ± 13.7	0.8626
Peak blood glucose, mg/dL	222.2 ± 36.2	249.1 ± 62.1	0.0882
Minimum Hct, %	22.0 ± 3.5	21.7 ± 2.9	0.6910
Mean CPB flow, mL/minute	3746.5 ± 461.4	3798.2 ± 576.2	0.7400

CPB indicates cardiopulmonary bypass; LVEF, left ventricular ejection fraction; and CPR, cardiopulmonary resuscitation.

for the postoperative GPL and the total ischemic time of the donor heart, so only the postoperative GPL was excluded as a factor from the multivariate analysis. We ultimately subjected two factors (total ischemic time of the donor heart and duration of preoperative LVAD support) to our multivariate analysis. Both the total ischemic time of the donor heart (OR, 1.0176; 95% CI, 1.0004-1.0375; *P* = 0.0444) and the duration of preoperative LVAD support (OR, 0.9977; 95% CI, 0.9952-0.9997; *P* = 0.0218) were found to be independent risk factors for HL after HTx.

The post-transplant outcomes are shown in Table V. Postoperative pulmonary complications occurred more frequently in the HL group than in the NHL group (24.1% versus 0%, *P* = 0.0322) due to the longer duration of intubation in the HL group (46.2 ± 59.2 versus 15.2 ± 11.2, *P* = 0.025). There were no significant differences between the two groups with regard to graft dysfunction. No hospital deaths occurred in either group.

Table III. The Postoperative Data

Variable	NHL (<i>n</i> = 20)	HL (<i>n</i> = 29)	<i>P</i>
Peak blood glucose, mg/dL	215 ± 38.9	242.2 ± 48.6	0.0425
GPL, mg/dL	176.0 ± 42.6	222.0 ± 60.8	0.0053
Dopamine, µg/kg/minute	4.7 ± 3.0	4.8 ± 2.1	0.9169
Dobutamine, µg/kg/minute	5.4 ± 2.2	5.1 ± 2.3	0.6816
Epinephrine, µg/kg/minute	0.08 ± 0.25	0.11 ± 0.33	0.7511
Norepinephrine, µg/kg/minute	0.6 ± 1.2	0.7 ± 1.4	0.8228
Epinephrine use, <i>n</i> (%)	2 (10.0)	3 (10.3)	1.0
Mechanical support, <i>n</i> (%)	1 (5.0)	5 (17.2)	0.3794
Amount of insulin*, U	25.4 ± 24.6	40.5 ± 36.5	0.1138

GPL indicates glucose at the time of peak lactate level; and*, Amount of insulin during the first 24 hours in the intensive-care unit.

Table IV. Correlation Matrix with Significance Levels (*P* Value) for Factors Significantly Associated with HL after Surgery on Univariate Analysis

Factor	Postoperative glucose at peak lactate levels	Duration of preoperative LVAD support	Total ischemic time of the donor heart
Postoperative glucose at peak lactate levels	1.0000 (< 0.0001)	-0.1214 (0.4113)	0.3070 (0.0319)
Duration of preoperative LVAD support	-0.1214 (0.4113)	1.0000 (< 0.0001)	-0.1484 (0.3143)
Total ischemic time of the donor heart	0.3070 (0.0319)	-0.1484 (0.3143)	1.0000 (< 0.0001)

HL indicates hyperlactatemia; and LVAD, left ventricular assist device support.

Table V. The Outcomes

Variable	NHL (<i>n</i> = 20)	HL (<i>n</i> = 29)	<i>P</i>
Pulmonary complication, <i>n</i> (%)	0 (0)	7 (24.1)	0.0322
Renal complication, <i>n</i> (%)	4 (20)	8 (27.6)	0.7377
Neurological complication, <i>n</i> (%)	2 (10.0)	3 (10.3)	1.0000
Graft dysfunction, <i>n</i> (%)	0 (0)	2 (6.9)	0.5068
Hospital stay, days	79.8 ± 130.7	61.4 ± 40.8	0.4808
Hospital mortality, <i>n</i> (%)	0 (0)	0 (0)	

CPB indicates cardiopulmonary bypass; and Hct, hematocrit.

Discussion

The main findings of the present study were as follows: (1) HL occurred after HTx in 59.2% of this population, (2) HL appears to be independently associated with the total ischemic time of the donor heart and the duration of preoperative LVAD support, and (3) HL is not associated with unfavorable outcomes other than pulmonary complications.

The incidence of HL in our study was almost the same as that of previous studies;¹¹⁾ however, it was thought to be higher than the incidence reported in previous studies on general heart surgery.^{6,12)} Hsu, *et al.*¹³⁾ reported that HL occurred in 12 of 58 patients (21%). As the cutoff level of HL was 15 mmol/L in that study, the incidence in their population might have been higher given the difference in the cutoff level. We also considered the possibility that their population might have included patients in an unstable cardiopulmonary state prior to surgery (preoperative use of IABP, *n* = 5; ECMO, *n* = 2, maximum preoperative lactate level, 3.1 mmol/L), as their report included four cases of hospital mortality (4 of 12, 33%).

According to previous reports, the risk factors for HL in both HTx and general cardiac surgery are related to the

duration of CPB, the duration of surgery, the intraoperative use of vasopressors, the maximum dose of inotropic drugs during the reperfusion phase and 12-24 hours after surgery, and the duration of inotrope use.^{6,11,14)} In the present study, we found no significant difference between the groups with regard to the maximum dose of inotropic drugs during the reperfusion phase and at 12-24 hours after surgery, the duration of CPB, the duration of surgery, or the duration of inotrope use. However, these factors were not significant in our study because the heart function is maintained in patients after HTx, and in many cases, the circulation dynamics are stable. Nixon, *et al.* reported on the association between preoperative mechanical support and HL.¹¹⁾ They found that HL was caused by a longer ischemic time due to complicated redo surgery, such as cases in which an LVAD was used. In our study, except for one case, an LVAD was implanted in all cases prior to HTx. The multivariate analysis revealed that both the total ischemic time of the donor heart and the duration of pretransplant LVAD were independent risk factors for HL after HTx. These findings suggest that HL may be caused by lactate flowing out of the graft. During cardiac surgery, lactate is measured from the coronary sinus after reperfusion of the heart over time, Chowdhury, *et al.* reported that lactate increased as myocardial damage

strengthened.¹⁵⁾ This suggests that lactate accumulates in the heart as a result of the slow progression of myocardial injury, despite being stored in cooled cardiac preservation solution. Lactate then flows throughout the body after reperfusion, and HL is observed in arterial blood. The results of this study suggest that with this degree of HL, metabolic disorders leading to cardiac dysfunction and multiple organ disorder can be avoided.

We consider the association between HL and the shorter duration of the LVAD support to be due to instability of the heart failure condition before transplantation. First, as reported by Mohacsi, *et al.*, exercise tolerance declines in patients with heart failure and tends to produce lactic acid.¹⁴⁾ Heart failure patients, even those with a preserved cardiac output (cardiac index > 2 l/minute/m²), can have a severe reduction in their peak oxygen consumption in preoperative spiroergometry. Poor exercise tolerance is due to early anaerobic metabolism. These patients are expected to have similar metabolic tendencies after transplantation and are likely to develop HL after transplantation. Regarding the characteristics of the donor hearts, although left ventricular hypertrophy (left ventricular wall thickness) and the body weight ratio were not considered, differences between the groups were observed in the total ischemic time of the donor heart, and there is a possibility that marginal donor hearts were used more frequently in the HL group (Table II). In other words, patients whose heart failure status before transplantation was unstable, may have been performed HTx earlier using marginal donor hearts, and as a result, the possibility that pretransplant LVAD support became shorter was considered. However, regarding patient characteristics, no right-sided heart catheters were inserted nor was spiroergometry performed immediately before transplantation, and further examinations of exercise tolerance are needed before surgery.

The results of this study indicate that the duration of intubation was significantly longer in the HL group than in the NHL group, and pulmonary complications were more frequent. However, HL is transient after surgery and recovered to the normal range within 24 hours. As such, a direct effect of HL on pulmonary complications is unlikely. Therefore, we speculate that short-term LVAD support, which is the determinant factor of HL, is associated with pulmonary complications. The mechanism underlying this relationship is thought to be the existence of heart failure before transplantation. Kinugawa, *et al.* reported that exercise intolerance related to skeletal muscle adversely affects not only prognosis but also quality of life in patients with heart failure.¹⁶⁾ There is also a report such as respiratory dysfunction after transplantation due to deconditioning of the respiratory muscles before transplantation.¹⁷⁾ Moreover, Mayer, *et al.* reported that patients with heart failure had a decreased respiratory muscle function, which was associated with their prognosis.¹⁸⁾ We therefore hypothesize that patients with heart failure who have low exercise tolerance because of a low respiratory muscle function tend to develop postoperative HL and may be prone to pulmonary complications.

We were unable to assess the involvement of systemic tissue hypoxia, as we did not examine the intracellular NAD⁺/NADH ratio. Further studies are therefore

needed to determine the metabolic state of systemic tissue using microdialysis in HTx patients.

Clinical implications: HL is associated with the total ischemic time of the donor heart and the duration of preoperative LVAD support. The former is one of the indicators that characterize the donor heart, and the latter is considered to be one of the indicators of preoperative heart failure status. HL is a good marker of the total ischemic time of the donor heart and the duration of preoperative LVAD support, and it can predict pulmonary complications after transplantation.

Study limitations: The present study is associated with two limitations: the study was retrospective in nature and was based on a single hospital experience; thus, these findings may not be generalizable.

Conclusion

We found that HL was common after HTx. The total ischemic time of the donor heart and the duration of preoperative LVAD support were risk factors for HL after HTx. Further prospective studies are needed to confirm the association between HL and both of donor heart ischemia and heart failure status before transplantation.

Disclosures

Conflicts of interest: The authors declare no conflicts of interest in association with the present study.

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