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Influence of intraoperative oxygen content on early postoperative graft dysfunction in living donor liver transplantation

A STROBE-compliant retrospective observational study

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Abstract

The aim of the present study was to investigate the role of intraoperative oxygen content on the development of early allograft dysfunction (EAD) in patients undergoing living donor liver transplantation (LDLT).

This retrospective review included 452 adult patients who underwent elective LDLT. Our study population was classified into 2 groups: EAD and non-EAD. Arterial blood gas analysis was routinely performed 3 times during surgery: during the preanhepatic phase (ie, immediately after anesthetic induction); during the anhepatic phase (ie, at the onset of hepatic venous anastomosis); and during the neohepatic phase (ie, 1 hour after graft reperfusion). Arterial oxygen content (milliliters per deciliters) was derived using the following equation: (1.34 × hemoglobin [gram per deciliters] × SaO_2 [%] × 0.01) + (0.0031 × PaO_2 [mmHg]).

The incidence of EAD occurrence was 13.1% (n = 59). Although oxygen contents at the preanhepatic phase were comparable between the 2 groups, the oxygen contents at the anhepatic and neohepatic phases were lower in the EAD group than in the non-EAD group. Patients with postoperative EAD had lower oxygen content immediately before and continuously after graft reperfusion, compared to patients without postoperative EAD. After the preanhepatic phase, oxygen content decreased in the EAD group but increased in the non-EAD group. The oxygen content and prevalence of normal oxygen content gradually increased during surgery in the non-EAD group, but not in the EAD group. Multivariable analysis revealed that oxygen content during the anhepatic phase and higher preoperative CRP levels were factors independently associated with the occurrence of EAD (area under the receiver-operating characteristic curve: 0.754; 95% confidence interval: 0.681–0.826; $P < .001$ in the model). Postoperatively, patients with EAD had a longer duration of hospitalization, higher incidences of acute kidney injury and infection, and experienced higher rates of patient mortality, compared to patients without EAD.

Lower arterial oxygen concentration may negatively impact the functional recovery of the graft after LDLT, despite preserved hepatic vascular flow. Before graft reperfusion, the levels of oxygen content components, such as hemoglobin content, PaO_2, and SaO_2, should be regularly assessed and carefully maintained to ensure proper oxygen delivery into transplanted liver grafts.

Abbreviations: ATP = adenosine triphosphate, CRP = C-reactive protein, EAD = early allograft dysfunction, LDLT = living donor liver transplantation, PRBC = packed red blood cell.

Keywords: oxygen content, early allograft dysfunction, living donor liver transplantation

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Early allograft dysfunction (EAD) is characterized by a constellation of abnormal findings, such as persistent hyperbilirubinemia, coagulopathy, ascites, or encephalopathy after liver transplantation (LT); it is also affected by various patient and donor factors, such as higher model for end-stage liver disease scores and older donor age.[1] In living donor LT (LDLT), partial liver grafts are used to meet metabolic demands and to grow to fit the patient's body size; therefore, inappropriate graft size (ie, graft to recipient weight ratio of <0.8%) is regarded as a critical risk factor for EAD occurrence.[2] Other risk factors for EAD include increased preoperative bilirubin level, increased portal reperfusion pressure, and increased donor body mass index. The overall incidence of EAD after LDLT is 16% to 19%[3]; the risks of postoperative graft loss and patient mortality are higher in patients with EAD than in those without EAD.[1–3]

Oxygen plays an important role in energy production, such as during the generation of adenosine triphosphate (ATP), which is used for organ metabolic homeostasis. Prolonged hypoxia leads to decreased ATP production and subsequent development of irreversible tissue injury related to organ failure.[4] Tissue hypoxia occurs due to an imbalance between oxygen supply and demand; oxygen supply depends on circulatory blood flow and oxygen content, which is derived from hemoglobin level, oxygen partial pressure (PaO_2), and oxygen saturation level (SaO_2).[5] Among patients undergoing noncardiac surgery, 6.8% experienced hypoxemic episodes and 3.5% experienced severe hypoxemic events during surgery.[6] A balance between oxygen delivery and requirements is an important target of medical efforts to avoid organ dysfunction and long-term poor outcomes in critically ill patients.

Thus far, the clinical impact of intraoperative oxygen content on postoperative graft function recovery has not been fully studied in patients undergoing LDLT. The aim of the present study was to investigate the role of intraoperative oxygen content in the development of EAD after LDLT.

2. Patients and methods

2.1. Ethical considerations

The present study was approved by the Institutional Review Board of Seoul St. Mary's Hospital Ethics Committee, Korea (reference No. KC19RESI0214) on April 15, 2019, and was performed in accordance with the tenets of the Declaration of Helsinki. The requirement for informed consent was waived by the review board due to the retrospective nature of the study.

2.2. Study population

This retrospective review included the data of 596 adult patients (age ≥19 years) who underwent elective LDLT between January 2009 and December 2018; the data were reviewed using the hospital electronic medical records system. Exclusion criteria were emergency surgery, a history of packed red blood cell (PRBC) transfusion within 1 week before surgery, and abnormal lung findings on chest x-ray and/or computed tomography images; these conditions seem to affect preoperative circulatory oxygen availability, including hemoglobin content, PaO_2, and SaO_2. Patients with incomplete or deficient data regarding clinical variables were also excluded from the analysis. A total of 144 patients were excluded; thus, data from 452 adult patients undergoing elective LDLT were analyzed in our study.

2.3. LDLT

The surgical procedure and anesthetic management for LDLT were previously described in detail.[7,8] In summary, the right hepatic lobe of a living donor was transplanted into the recipients using the piggyback technique. Anastomoses of hepatic vessels were performed (ie, the hepatic vein, portal vein, and hepatic artery in a serial manner) and the patency of hepatic vascular flow was confirmed using Doppler ultrasonography (Prosound SSD-5000; Hitachi Aloka Medical, Tokyo, Japan).

Balanced anesthesia was induced with multiple invasive monitoring modalities. Based on the Practice Guidelines for Perioperative Blood Management,[9] PRBC and coagulation factors (ie, fresh frozen plasma, single donor platelets, and cryoprecipitates) were replaced based on laboratory measurements (ie, a hematocrit level of ≥25%). Ventilator care was adjusted for adequate oxygenation (ie, SaO_2 ≥95%) and normocarbia (ie, end-tidal CO_2 of 30–40 mmHg); hemodynamic stability (ie, mean blood pressure ≥65 mmHg and central venous pressure ≤10 mmHg) was maintained by appropriate fluid resuscitation and vasopressor infusion, based on the clinical judgment of attending anesthesiologists.

The immunosuppression regimen included calcineurin inhibitor, mycophenolate mofetil, and prednisolone. Basiliximab was administered before surgery and on postoperative day 4. Immunosuppressant drugs were gradually tapered after surgery.

2.4. Arterial blood gas analysis

Arterial blood gas analysis was routinely performed 3 times during surgery: during the preanhepatic phase (ie, immediately after anesthetic induction); during the anhepatic phase (ie, at the onset of hepatic venous anastomosis); and during the neohepatic phase (ie, 1 hour after graft reperfusion). Additional arterial blood gas analysis was performed as needed during surgery, based on the clinical judgment of attending anesthesiologists. Arterial blood samples were collected without stasis and bubbles into heparin-coated syringes (BD Preset, Plymouth, UK), then assessed using a point-of-care test with an ABL800 FLEX blood gas analyzer (Radiometer, Brønshøj, Denmark). Arterial oxygen content (milliliters per deciliters) was derived from the measurement of the concentration of oxygen, which is carried by hemoglobin and dissolved in blood, using the following equation: $(1.34 \times \text{hemoglobin [gram per deciliters]} \times SaO_2\ [\%] \times 0.01) + (0.0031 \times PaO_2\ [\text{mmHg}])$. The clinically accepted normal range of arterial oxygen content is 17 to 20 mL/dL.[5]

2.5. EAD

EAD was defined by one of the following conditions: total bilirubin ≥10 mg/dL on postoperative day 7; international normalized ratio ≥1.6 on postoperative day 7; and alanine and/or aspartate aminotransferase >2000 IU/mL within 7 days postoperatively.[1,3] Using these data, the study population was classified into 2 groups—EAD and non-EAD.

2.6. Perioperative recipient and donor-graft findings

Preoperative recipient findings included age, sex, body mass index, comorbidity (ie, diabetes mellitus and hypertension), etiology, model for end-stage liver disease score, requirement of continuous renal replacement therapy, hepatic complications (ie, encephalopathy West-Haven grade I or II,[10] varices, and

ascites), transthoracic echocardiography (ie, ejection fraction and diastolic dysfunction[11]), and laboratory variables (ie, measurements of hemoglobin, C-reactive protein [CRP], white blood cell count, neutrophil to lymphocyte ratio, platelet count, international normalized ratio, creatinine, albumin, sodium, potassium, calcium, glucose, and ammonia). Intraoperative recipient findings included surgical duration, postreperfusion syndrome,[12] mean lactate level, average of vital signs (ie, mean blood pressure, heart rate, and central venous pressure), amounts of blood products transfused (ie, PRBCs, fresh frozen plasma, single donor platelets, and cryoprecipitates), hourly fluid infusion, and hourly urine output. Donor-graft findings included age, sex, body mass index, graft-recipient weight ratio, fatty percentage, total ischemic time, duration between anastomoses of portal vein and hepatic artery, and Doppler ultrasonography (ie, hepatic arterial resistive index and portal venous flow). Postoperative outcomes included hospital period, acute kidney injury,[13] infection (ie, positive blood cultures), and patient mortality.

2.7. Statistical analysis

The normality of continuous data was evaluated using the Shapiro-Wilk test. Continuous data were expressed as medians and interquartile ranges (IQRs) and categorical data were expressed as numbers and proportions. The perioperative recipient and donor-graft factors were compared between EAD and non-EAD groups using the Mann-Whitney U test (continuous data) and the χ^2 or Fisher exact test (categorical data), as appropriate. Intraoperative serial changes of oxygen content, hemoglobin, SaO_2, and PaO_2 were evaluated using the Friedman test with the Wilcoxon signed-rank test as a post hoc test. After dividing oxygen contents into normal versus low based on a cutoff value of 17 mL/dL, intraoperative changes in the proportions of patients with normal oxygen contents were analyzed using Cochran's Q test with the McNemar test as a post hoc test. The associations of perioperative recipient and donor-graft factors with the development of EAD were investigated using univariable and multivariable logistic regression analyses. Potentially valid factors ($P \leq .1$) in univariable analysis were entered into multivariable forward and backward regression analyses. The values were expressed as odds ratios with 95% confidence intervals (CIs). When correlations with multiple perioperative factors were present, the most clinically critical factors were selected. The accuracy of the model for EAD was investigated using the area under the receiver-operating characteristic curve (AUC). All tests were 2-sided, and $P < .05$ was considered statistically significant. Statistical analyses were performed using SPSS (ver. 22 for Windows; IBM Corp., Armonk, NY) and MedCalc (ver. 11 for Windows; MedCalc Software, Mariakerke, Belgium).

3. Results

3.1. Demographic features of the study population

The study population included 315 men (69.7%) and 137 women (30.3%). The median (IQR) age and body mass index were 54 (49–59) years and 23.9 (21.9–26.4) kg/m^2, respectively. The median (IQR) model for end-stage liver disease score was 12 (6–23) points. The most common cause for LDLT was hepatitis B (57.3%), followed by alcoholic hepatitis (19.2%), hepatitis C (7.1%), autoimmune hepatitis (4.9%), hepatitis A (4.0%), toxic hepatitis (2.2%), and cryptogenic hepatitis (5.3%). The incidence of EAD occurrence was 13.1% (n = 59 patients). The median (IQR) oxygen contents at each surgical phase were 13.1 (11.9–14.4) mL/dL during the preanhepatic phase, 13.7 (11.8–16.2) mL/dL during the anhepatic phase, and 13.7 (12.3–15.2) mL/dL during the neohepatic phase. Based on the normal range of oxygen content, the proportions of normal oxygen content were 3.3% (n = 15 patients) at the preanhepatic phase, 19.2% (n = 87 patients) at the anhepatic phase, and 9.3% (n = 42 patients) at the neohepatic phase.

3.2. Preoperative and intraoperative recipient and donor-graft findings in patients with/without postoperative EAD

The analysis of preoperative recipient findings (Table 1) revealed that the EAD group required more continuous renal replacement therapy and exhibited higher levels of inflammatory biomarkers (ie, CRP, white blood cell count, and neutrophil to lymphocyte ratio) than the non-EAD group, whereas the platelet count was lower in the EAD group. The analysis of intraoperative recipient findings revealed that the average heart rate and amounts of blood product transfused (ie, PRBCs, fresh frozen plasma, and single donor platelets) were higher in the EAD group than in the non-EAD group, whereas hourly urine output was lower in the EAD group than in the non-EAD group. Analysis of donor-graft findings revealed no significant differences between the 2 groups.

3.3. Oxygen content, hemoglobin, SaO_2, and PaO_2 in patients with/without postoperative EAD

The analysis of intraoperative oxygen contents (Table 2, Figs. 1 and 2) revealed that patients with postoperative EAD had lower oxygen contents during the anhepatic and neohepatic phases, compared to patients without postoperative EAD. Hemoglobin content and PaO_2 during the anhepatic and neohepatic phases and SaO_2 during the anhepatic phase were lower in the EAD group than in the non-EAD group. The analysis of serial changes in oxygen content in each group revealed that oxygen content increased from the preanhepatic phase to the anhepatic and neohepatic phases in the non-EAD group; however, in the EAD group, the oxygen content decreased from the preanhepatic phase to the anhepatic and neohepatic phases. In the non-EAD group, hemoglobin content increased from the preanhepatic phase to the anhepatic and neohepatic phases; however, SaO_2 during the neohepatic phase and PaO_2 during the anhepatic phase were lower than their respective levels during the preanhepatic phase. In the EAD group, hemoglobin content, SaO_2, and PaO_2 during the anhepatic phase were lower than their respective levels during the preanhepatic phase.

3.4. Prevalence of normal range of oxygen content among surgical phases in patients with/without postoperative EAD

The analysis of the intraoperative prevalence of normal oxygen content (Table 3) revealed that the prevalence at the anhepatic phase was lower in the EAD group than in the non-EAD group. The analysis of serial changes of the prevalence of normal oxygen content in each group showed that the prevalence was higher at the anhepatic and neohepatic phases than at the preanhepatic phase in the non-EAD group; however, in the EAD group, there were no significant differences in prevalence between the preanhepatic phase and the anhepatic and neohepatic phases.

Table 1

Comparison of preoperative and intraoperative recipient and donor-graft findings in patients with/without postoperative early allograft dysfunction.

Group	Non-EAD	EAD	
n	393	59	*P*
Preoperative recipient finding			
Age, y	54 (49–60)	54 (49–56)	.299
Sex (no. of males)	278 (70.7%)	37 (62.7%)	.211
Body mass index, kg/m^2	23.9 (22.0–26.2)	24.2 (21.4–27.1)	.558
Comorbidity			
Diabetes mellitus	103 (26.2%)	12 (20.3%)	.334
Hypertension	78 (19.8%)	7 (11.9%)	.143
Etiology			.454
Alcoholic hepatitis	77 (19.6%)	10 (16.9%)	
Hepatitis A	14 (3.6%)	4 (6.8%)	
Hepatitis B	227 (57.8%)	32 (54.2%)	
Hepatitis C	27 (6.9%)	5 (8.5%)	
Toxic hepatitis	8 (2.0%)	2 (3.4%)	
Autoimmune hepatitis	17 (4.3%)	5 (8.5%)	
Cryptogenic hepatitis	23 (5.9%)	1 (1.7%)	
MELD score (point)	12 (6–23)	16 (7–29)	.087
Requirement of CRRT	71 (18.1%)	21 (35.6%)	.002
Hepatic complications			
Encephalopathy grade I or II	33 (8.4%)	7 (11.9%)	.382
Varix	90 (22.9%)	12 (20.3%)	.661
Ascites	172 (43.8%)	32 (54.2%)	.132
Transthoracic echocardiography			
Ejection fraction (%)	64.6 (62.0–67.0)	64.6 (62.9–67.0)	.82
Diastolic dysfunction	167 (42.5%)	22 (37.3%)	.45
Laboratory variables			
Hemoglobin, g/dL	10.0 (8.5–11.9)	9.3 (8.4–11.6)	.38
C-reactive protein, mg/dL	0.3 (0.1–1.0)	1.7 (0.3–4.8)	<.001
WBC count ($\times 10^9$ cells/L)	4.0 (2.7–5.9)	6.2 (3.8–10.7)	<.001
Neutrophil to lymphocyte ratio	2.4 (1.4–4.5)	5.9 (2.8–10.2)	<.001
Platelet count ($\times 10^9$ cells/L)	64.0 (46.5–108.5)	58.0 (35.0–85.0)	.024
International normalized ratio	1.4 (1.2–2.0)	1.6 (1.3–2.3)	.078
Creatinine, mg/dL	0.8 (0.7–1.1)	0.8 (0.7–1.4)	.332
Albumin, g/dL	3.0 (2.7–3.6)	3.0 (2.7–3.4)	.634
Sodium, mEq/L	140.0 (136.0–142.0)	139.0 (133.0–141.0)	.149
Potassium, mEq/L	4.0 (3.7–4.3)	3.9 (3.5–4.2)	.079
Calcium, mg/dL	8.4 (8.0–8.8)	8.3 (7.9–8.8)	.187
Glucose, mg/dL	106.0 (91.0–133.0)	115.0 (95.0–152.0)	.199
Ammonia, μg/dL	100.0 (66.5–157.5)	93.0 (68.0–156.0)	.618
Intraoperative recipient finding			
Surgical duration, min	510 (455–580)	510 (460–580)	.918
Postreperfusion syndrome	70 (17.8%)	15 (25.4%)	.163
Mean lactate level, mmol/L	3.8 (3.0–5.2)	3.9 (3.0–5.0)	.772
Mean oxygen content, mL/dL	13.6 (12.4–15.1)	12.7 (11.6–13.9)	.001
Average of vital signs			
MBP, mmHg	77 (71–85)	78 (68–86)	.713
HR, beats/min	88 (80–99)	95 (80–108)	.026
CVP, mmHg	9 (7–11)	9 (7–11)	.553
Blood product transfusion, U			
Packed red blood cells	7 (4–13)	10 (7–15)	.002
Fresh frozen plasma	7 (4–10)	10 (6–15)	<.001
Single donor platelets	1 (0–2)	1 (0–3)	.015
Cryoprecipitates	0 (0–0)	0 (0–0)	.367
Hourly fluid infusion, mL/kg/h	9.3 (6.5–12.4)	8.9 (6.1–12.5)	.777
Hourly urine output, mL/kg/h	1.4 (0.7–2.1)	1.1 (0.3–1.9)	.035
Donor-graft finding			
Age, y	31 (25–42)	35 (26–48)	.07
Sex (male)	246 (62.6%)	31 (52.5%)	.139
Body mass index, kg/m^2	23.5 (21.3–25.8)	23.5 (21.5–25.2)	.7
GRWR (%)	1.2 (1.0–1.4)	1.1 (0.9–1.4)	.162
Fatty percentage (%)	5 (0–5)	5 (0–5)	.931
Total ischemic time, min	92 (69–117)	104 (70–136)	.161
Duration between anastomoses of portal vein and hepatic artery, min	24 (22–26)	25 (23–26)	.389
Doppler ultrasonography			
Hepatic arterial resistive index	0.64 (0.61–0.68)	0.63 (0.60–0.67)	.466
Portal venous flow, mL/min	2180 (1562–2344)	2179 (1414–2278)	.628

CRRT = continuous renal replacement therapy, CVP = central venous pressure, EAD = early allograft dysfunction, GRWR = graft-recipient weight ratio, HR = heart rate, MBP = mean blood pressure, MELD = model for end-stage liver disease, WBC= white blood cell count.

Values are expressed as median (interquartile range) and number (proportions).

Table 2

Comparison of oxygen content, hemoglobin content, SaO_2, and PaO_2 in patients with/without postoperative early allograft dysfunction.

Group N	Non-EAD 393	EAD 59	*P*
Oxygen content, mL/dL			
Preanhepatic phase	13.1 (11.9–14.4)	13.2 (11.9–14.9)	.691
Anhepatic phase	14.1 (12.0–16.4)***	11.8 (10.8–13.8)*	<.001
Neohepatic phase	13.9 (12.4–15.4)***	12.5 (11.8–14.1)	.002
Hemoglobin, g/dL			
Preanhepatic phase	9.4 (8.5–10.4)	9.5 (8.4–10.8)	.6
Anhepatic phase	10.1 (8.6–11.9)***	8.7 (7.8–10.1)*	<.001
Neohepatic phase	9.9 (8.9–11.1)***	9.0 (8.3–10.3)	.002
SaO_2 (%)			
Preanhepatic phase	99.4 (98.9–99.7)	99.3 (99.0–99.6)	.854
Anhepatic phase	99.4 (98.7–99.7)	99.0 (98.2–99.5)*	.01
Neohepatic phase	99.3 (98.9–99.5)***	99.3 (99.0–99.5)	.831
PaO_2, mmHg			
Preanhepatic phase	196.0 (166.5–228.0)	189.0 (151.0–219.0)	.222
Anhepatic phase	177.0 (130.5–214.0)***	132.0 (110.0–171.0)***	<.001
Neohepatic phase	199.0 (171.5–230.0)	184.0 (151.0–215.0)	.033

Values are expressed as medians with interquartile ranges in parentheses. EAD = early allograft dysfunction, PaO_2 = oxygen partial pressure, SaO_2 = oxygen saturation level.
* $P < .05$ versus the level during the preanhepatic phase.
** $P < .01$ versus the level during the preanhepatic phase.
*** $P < .001$ versus the level during the preanhepatic phase.

3.5. Associations of preoperative and intraoperative clinical factors with postoperative EAD

Univariable analysis (Table 4) revealed that preoperative recipient findings (ie, model for end-stage liver disease score, requirement of continuous renal replacement therapy, CRP, white blood cell count, neutrophil to lymphocyte ratio, and platelet count), intraoperative recipient findings (ie, oxygen contents at the anhepatic and neohepatic phases; average heart rate; total transfusion amount of PRBCs, fresh frozen plasma, and single donor platelets; and hourly urine output), and donor-graft findings (ie, age and total ischemic time) were potentially associated with postoperative EAD. In multivariable analysis, a model that included oxygen content during the anhepatic phase and CRP level before surgery was significantly associated with postoperative EAD (AUC: 0.754; 95% CI: 0.681–0.826; $P < .001$ in the model).

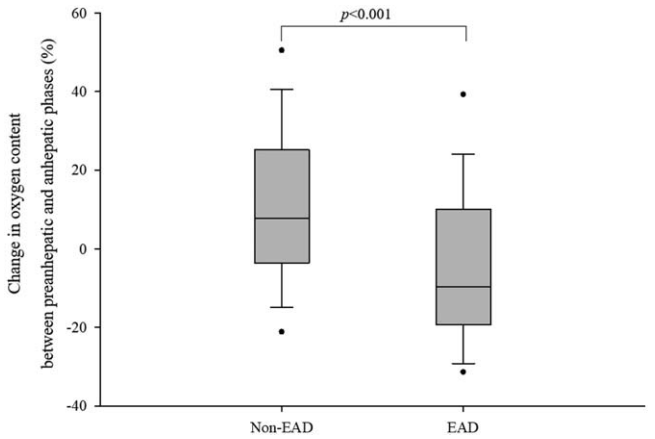

Figure 1. Comparison of changes in oxygen content between the preanhepatic and anhepatic phases in patients with/without postoperative early allograft dysfunction (EAD).

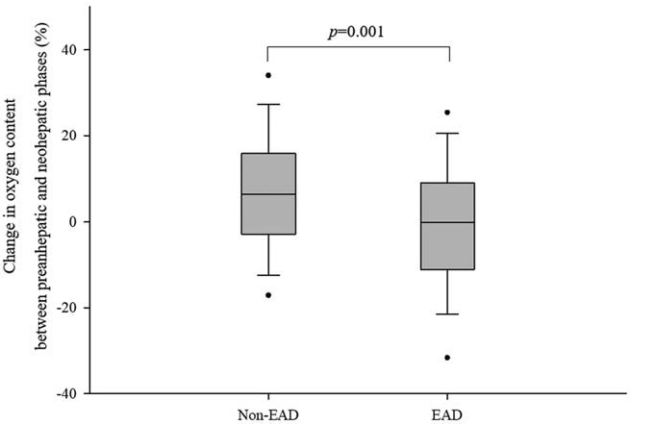

Figure 2. Comparison of changes in oxygen content between the preanhepatic and neohepatic phases in patients with/without postoperative early allograft dysfunction (EAD).

3.6. Postoperative outcomes in patients with/without postoperative EAD

The median (IQR) length of hospitalization was longer in the EAD group (32 [23–56] days) than in the non-EAD group (25 [21–34] days; $P = .001$). Incidences of acute kidney injury (non-EAD: 26.2%; EAD: 47.5%; $P = .001$) and infection (non-EAD: 6.6%; EAD: 18.6%; $P = .004$) were higher in the EAD group than in the non-EAD group. During the follow-up period (median: 4 years; IQR: 1–7 years), the frequency of patient mortality was worse in the EAD group (33.9%) than in the non-EAD group (12.5%; $P < .001$).

4. Discussion

The main finding in our study was that intraoperative systemic oxygen content affected early postoperative graft recovery in

Table 3

Prevalence of normal range of oxygen content at each surgical phase in patients with/without postoperative early allograft dysfunction.

Group N	Non-EAD 393	EAD 59	*P*
Oxygen content			
Preanhepatic phase			1.000
Normal range	13 (3.3%)	2 (3.4%)	
Low range	380 (96.7%)	57 (96.6%)	
Anhepatic phase			0.003
Normal range	84 (21.4%)	3 (5.1%)	
Low range	309 (78.6%)***	56 (94.9%)	
Neohepatic phase			0.094
Normal range	40 (10.2%)	2 (3.4%)	
Low range	353 (89.8%)***	57 (96.6%)	

Values are expressed as numbers with percentages in parentheses. EAD = early allograft dysfunction.
* $P < .05$ vs the level during the preanhepatic phase.
** $P < .01$ vs the level during the preanhepatic phase.
*** $P < .001$ vs the level during the preanhepatic phase.

Table 4

Associations of preoperative and intraoperative clinical factors with postoperative early allograft dysfunction.

	Univariable logistic regression				Multivariable logistic regression			
	ß	Odds ratio	95% CI	*P*	*ß*	Odds ratio	95% CI	*P*
Preoperative recipient finding								
Age, y	−0.011	0.989	0.959–1.021	.503				
Sex (male vs female)	0.363	1.437	0.812–2.543	.213				
Body mass index, kg/m^2	0.031	1.032	0.959–1.110	.398				
Comorbidity								
Diabetes mellitus	−0.33	0.719	0.367–1.408	.336				
Hypertension	−0.609	0.544	0.238–1.243	.149				
MELD score (point)	0.026	1.026	1.002–1.052	.037	−0.029	0.972	0.936–1.009	.14
Requirement of CRRT	0.919	2.506	1.387–4.529	.002	0.398	1.489	0.69–3.211	.31
Hepatic complications								
Encephalopathy grade I or II	0.384	1.469	0.618–3.491	.384				
Varix	−0.151	0.860	0.437–1.690	.661				
Ascites	0.421	1.523	0.879–2.638	.134				
Transthoracic echocardiography								
Ejection fraction (%)	0.014	1.014	0.953–1.079	.654				
Diastolic dysfunction	−0.217	0.805	0.458–1.415	.450				
Laboratory variables								
Hemoglobin, g/dL	−0.05	0.952	0.841–1.077	.433				
C-reactive protein, mg/dL	0.448	1.565	1.358–1.803	<.001	0.382	1.464	1.265–1.696	<.001
WBC count (×10^9 cells/L)	0.111	1.118	1.064–1.174	<.001	0.044	1.045	0.975–1.119	.217
Neutrophil to lymphocyte ratio	0.057	1.058	1.019–1.100	.004	−0.009	0.991	0.951–1.032	.651
Platelet count (×10^9 cells/L)	−0.006	0.994	0.988–1.000	.054	−0.005	0.995	0.988–1.002	.139
International normalized ratio	0.226	1.254	0.937–1.677	.128				
Creatinine, mg/dL	0.041	1.041	0.864–1.255	.670				
Albumin, g/dL	−0.151	0.860	0.533–1.387	.536				
Sodium, mEq/L	−0.028	0.972	0.925–1.022	.274				
Potassium, mEq/L	−0.331	0.718	0.437–1.180	.191				
Calcium, mg/dL	−0.199	0.819	0.546–1.230	.336				
Glucose, mg/dL	0.001	1.001	0.996–1.005	.804				
Ammonia, μg/dL	−0.001	0.999	0.995–1.002	.442				
Intraoperative recipient finding								
Surgical duration, min	0.000	1.000	0.997–1.002	.755				
Postreperfusion syndrome	0.453	1.573	0.829–2.985	.166				
Mean lactate, mmol/L	−0.058	0.943	0.816–1.091	.431				
Oxygen content, mL/dL								
Preanhepatic phase	0.079	1.082	0.962–1.218	.190				
Anhepatic phase	−0.261	0.77	0.689–0.862	<.001	−0.17	0.844	0.748–0.952	.006
Neohepatic phase	−0.162	0.851	0.758–0.955	.006	0.32	1.032	0.886–1.203	.685
Average of vital signs								
MBP, mmHg	−0.001	0.999	0.990–1.009	.911				
HR, beats/min	0.025	1.025	1.006–1.045	.009	0.014	1.014	0.992–1.036	.212
CVP, mmHg	−0.032	0.969	0.885–1.060	.490				
Blood product transfusion, U								
Packed red blood cells	0.036	1.037	1.006–1.068	.019	−0.005	0.995	0.95–1.043	.849
Fresh frozen plasma	0.057	1.059	1.025–1.094	.001	0.028	1.028	0.973–1.087	.325
Single donor platelets	0.074	1.076	0.992–1.168	.078	0.018	1.019	0.908–1.142	.752
Cryoprecipitates	0.051	1.052	0.921–1.202	.452				
Hourly fluid infusion, mL/kg/h	0.003	1.003	0.977–1.029	.836				
Hourly urine output, mL/kg/h	−0.272	0.762	0.575–1.010	.059	−0.059	0.943	0.668–1.331	.737
Donor-graft finding								
Age, y	0.021	1.021	0.999–1.043	.065	0.017	1.017	0.992–1.043	.174
Sex (male vs female)	0.413	1.512	0.872–2.621	.141				
Body mass index, kg/m^2	−0.034	0.966	0.885–1.055	.446				
GRWR (%)	0.191	1.21	0.561–2.613	.627				
Fatty percentage (%)	−0.014	0.986	0.942–1.032	.540				
Total ischemic time, min	0.004	1.004	1.001–1.008	.025	0.000	1.000	0.996–1.004	.95
Duration between anastomoses of portal vein and hepatic artery, min	0.043	1.044	0.944–1.154	.404				
Doppler ultrasonography								
Hepatic arterial resistive index	−1.976	0.139	0.003–5.775	.299				
Portal venous flow, mL/min	0.000	1.000	1.000–1.000	.971				

CRRT = continuous renal replacement therapy, CVP = central venous pressure, GRWR = graft-recipient weight ratio, HR = heart rate, MBP = mean blood pressure, MELD = model for end-stage liver disease, WBC = white blood cell.

patients undergoing LDLT. Patients with postoperative EAD had lower oxygen content immediately before and continuously after graft reperfusion, compared to patients without postoperative EAD. After the preanhepatic phase, oxygen content decreased in the EAD group but increased in the non-EAD group. Multivariable analysis revealed that oxygen content during the anhepatic phase and higher preoperative CRP levels were factors independently associated with the occurrence of EAD. Postoperatively, patients with EAD had a longer duration of hospitalization, higher incidences of acute kidney injury and infection, and experienced higher rates of patient mortality, compared to patients without EAD.

Our results suggest that lower systemic oxygen content is associated with impaired graft functional recovery after LDLT. Hepatic in-flow circulation consists of a dual blood supply in which 75% of blood flow is from the portal vein and 25% is from the hepatic artery; in the hepatic oxygen supply, 50% of oxygenation is contributed by the portal vein and 50% is contributed by the hepatic artery.[14] Oxygen availability is a key aspect of the cellular microenvironment and is related to functional and metabolic balance. In particular, highly metabolic organs such as the liver require appropriate oxygen supply for parenchymal durability.[15] Because of the hepatic anatomic structure, oxygen concentration progressively decreases through the sinusoids (from the periportal zone to the perivenous zone); lower oxygen delivery in the perivenous zone is associated with increased vulnerability for hypoxia-induced hepatocyte injury.[16] Because oxygen serves as a regulator of hepatic metabolic processes, hepatocyte oxygen availability before stress predominantly affects patient and/or post-stress graft outcomes.[17,18] In experimental studies related to liver oxygen supply, early hyperbaric oxygen therapy played a protective role in reducing the severity of hepatocyte ischemia-reperfusion injury and fibrogenesis by decreasing oxidant stress, energy (ie, ATP) loss, necrosis, or apoptosis, as well as by improving microvascular patency.[19–22] After ischemia-reperfusion injury, oxygen therapy can secure hepatic homeostasis; this is characterized by the alleviation of neutrophil accumulation and activation, as well as by the improvement of mitochondrial function.[23,24] Additionally, oxygen therapy facilitated hepatocyte proliferation and regeneration through improvements in angiogenesis, antioxidant activity, transporter and mitochondrial function, and energy metabolism stability.[25–28] In an LT study by Fukazawa et al,[29] the graft reperfusion phase was classified as stages of hepatic revascularization as follows: phase 1 (from portal vein reperfusion to 5 minutes after portal vein reperfusion); phase 2 (from 5 minutes after portal vein reperfusion to hepatic artery reperfusion); and phase 3 (from hepatic artery reperfusion to 3 hours after portal vein reperfusion). In liver graft oxygenation after reperfusion, lower systemic oxygen content may result in low oxygen availability in a transplanted graft, particularly between anastomoses in the portal vein and hepatic artery, as well as continuously after restoration of the dual blood supply. Therefore, a deficient amount of systemic oxygen may impair the achievement of an appropriate oxygen level to meet the graft metabolic demand, eventually affecting posttransplant graft functional recovery in patients undergoing LDLT.

Clinically, PRBC transfusion is regarded as a treatment option to improve arterial oxygen delivery and provide adequate tissue oxygen.[30] However, intraoperative PRBC transfusion is considered a poor prognostic factor in the LT setting. An increased requirement of PRBC transfusion during surgery was associated with negative postoperative outcomes, such as a longer hospital stay and worse patient and graft survival.[31,32] In LDLT, massive intraoperative PRBC transfusion (ie, ≥10 U) was an independent risk factor for in-hospital mortality in patients with a high model for end-stage liver disease score (ie, ≥20 points).[33] EAD occurred more frequently in patients who required more PRBC transfusions than in those who required fewer transfusions.[34] The negative outcomes of PRBC transfusions may be associated with hazard variables such as the antigen-antibody immunologic reaction, viral and/or bacterial transmission, and transfusion-related lung and/or kidney injury.[35] In previous LT studies,[36–38] patients with a higher requirement for intraoperative PRBC transfusion had lower preoperative hemoglobin levels than patients with a lower requirement for PRBC transfusion. However, in our study, patients who had received a PRBC transfusion within 1 week before surgery were excluded to avoid the influence of preoperative PRBC transfusion on patient and graft outcomes; therefore, preoperative hemoglobin and preanhepatic oxygen content, including hemoglobin content, were comparable between the 2 groups. Although the EAD group received a larger intraoperative transfusion of PRBC compared to the non-EAD group, the systemic oxygen concentration in the EAD group was predominantly lower throughout the surgical phases. Thus far, the appropriate balance between PRBC transfusion and oxygen concentration for graft recovery has been uncertain. Small grafts, such as those used in LDLT, need to grow to an adequate size relative to the patient's body size and satisfy the patient's metabolic demands; thus, a lower oxygen concentration may impair the provision of appropriate oxygen availability in the graft microenvironment. Eventually, considering the negative impact of allogeneic PRBC transfusion on immunological reactions and patient survival, intraoperative blood salvage autotransfusion (ie, cell saver) could be used to minimize the need for perioperative transfusion of allogeneic blood and maintain circulatory oxygen availability during LT.[39,40]

Respiratory practice (ie, fraction of inspired oxygen) was able to modulate oxygen parameters, such as SaO_2 and PaO_2. However, potential oxygen toxicity may arise in the liver, primarily related to free-radical chain reactions and reactive oxygen species, leading to hepatocytic death.[41,42] Oxygen toxicity plays a role in the interruption of hepatic biosynthesis functions, such as reduced activity levels of succinic dehydrogenase and cytochrome oxidase; however, an antioxidant regimen (ie, vitamins C and E) can be used to offset oxidative stress in the liver.[43,44] Oxygen toxicity is reported to develop under the condition of ≥3 atmosphere absolute; therefore, in clinical settings (ie, 1 atmosphere absolute), oxygen toxicity-induced cell injury may be quite scarce.[45] Nevertheless, thus far, specific anesthetic respiratory care to prevent pulmonary complications has not been available, and the appropriate oxygen fraction and duration related to graft recovery have not been fully investigated in patients undergoing LDLT. Although our study populations received lung protective ventilator care during surgery, and those with preoperative abnormal lung findings were excluded, oxygen parameters (ie, SaO_2 and PaO_2) were worse in the EAD group than in the non-EAD group. Eventually, it will be necessary to perform early stratification of patients at high risk due to intraoperative poor oxygen availability, to improve patient and graft outcomes in LDLT.

The occurrence of EAD is related to various factors, including inflammatory activation and oxidative stress in response to

ischemia-reperfusion graft injury during LT.[46,47] Considering the major role of inflammation in EAD development, preoperative inflammatory conditions in LDLT patients may be critical for graft functional recovery.[48,49] Clinically, CRP has been accepted as an acute-phase inflammatory reactant and a predictor for morbidity and mortality after major surgery.[50] Increased CRP levels are independently predictive of accelerated decline of graft function after kidney transplantation.[51] In an LT study, a higher CRP level (ie, ≥1 mg/dL) before surgery was significantly associated with the risks of hepatocellular carcinoma recurrence and patient mortality.[52] In an LDLT study, patients with CRP levels ≥1.0 mg/dL exhibited worse survival than those with CRP levels <1.0 mg/dL.[53] Our results suggested that preoperative CRP level (reflective of inflammation status) has an independent relationship with EAD occurrence and supported previous reports regarding the prognostic role of CRP for posttransplant outcomes.[52,53]

There were some limitations in our study. First, we were unable to correctly measure the intraoperative amount of hemorrhage during each surgical phase because of the large amounts of ascites and irrigation fluid. Keeping a meticulous balance between hemorrhage and blood transfusion may play a critical role in the maintenance of circulatory oxygen delivery and the reduction of redundant blood transfusions. Second, we were unable to directly measure the oxygen content in the portal vein and hepatic artery. Because the liver is oxygenated by a dual blood supply, the oxygen content in the radial artery largely reflects the oxygen content in the hepatic artery but does not reflect the oxygen content in the portal vein. Third, we were unable to measure the affinity of hemoglobin for oxygen. Because of the elevated level of 2,3-diphosphoglycerate in erythrocytes, cirrhotic patients exhibited a reduced capacity for oxygen binding by hemoglobin.[54] Therefore, the measured hemoglobin level may not directly represent arterial oxygen availability in patients undergoing LT.

In conclusion, lower arterial oxygen concentration may negatively impact graft function recovery after LDLT, despite the preservation of hepatic vascular flow. Before graft reperfusion, the levels of oxygen content components, such as hemoglobin content, PaO_2, and SaO_2, should be regularly assessed and carefully maintained to ensure proper oxygen delivery into transplanted liver grafts. Because allogeneic blood transfusion seems to have injurious complications, and appropriate respiratory therapy during surgery has not yet been established, blood salvage autotransfusion, such as using a cell saver device, is a potential safe and effective option for maintaining hemoglobin homeostasis during surgery. Further studies related to oxygen therapy for accelerated graft recovery are needed in patients undergoing LDLT.

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