Intraoperative High Fraction of Inspiratory Oxygen is Independently Associated with Worse Outcome After Living-Donor Liver Transplantation: A Retrospective Study

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Abstract

Background Ischemia and reperfusion injury is an important factor that determines graft function after liver transplantation, and oxygen plays a crucial role in this process. However, the relationship between the intraoperative high fraction of inspiratory oxygen (FiO2) and living-donor-liver-transplantation (LDLT) outcome remains unclear.

Patients and Methods A total of 199 primary adult-to-adult LDLT cases in Kyoto University Hospital between January 2010 and December 2017 were enrolled in this study. The intraoperative FiO2 was averaged using the total amount of intraoperative oxygen and air and defined as the calculated FiO2 (cFiO2). The cutoff value of cFiO2 was set at 0.5.

Results Between the cFiO2 <0.5 (n = 156) and ≥0.5 group (n = 43), preoperative recipients’ background, donor factors, and intraoperative parameters were almost comparable. Postoperatively, the cFiO2 ≥0.5 group showed a higher early allograft dysfunction (EAD) rate (P = 0.049) and worse overall graft survival (P = 0.036) than the cFiO2 <0.5 group. Although the cFiO2 ≥0.5 was not an independent risk factor for EAD in multivariable analysis (OR 2.038, 95%CI 0.992–4.186, P = 0.053), it was an independent risk factor for overall graft survival after LDLT (HR 1.897, 95%CI 1.007–3.432, P = 0.048).

Conclusion The results of this study suggest that intraoperative high FiO2 may be associated with worse graft survival after LDLT. Avoiding higher intraoperative FiO2 may be beneficial for LDLT recipients.

Introduction

In liver transplantation, ischemia and reperfusion injury (IRI) is one of the important factors that determine postoperative graft function [1]. The abrupt cessation of blood flow and subsequent ischemia decreases several antioxidants, such as glutathione, and also tissue adenosine triphosphate [2–4]. This ischemic phase itself damages the liver tissue [4]; moreover, after reperfusion, numerous cellular and molecular factors in various pathways are rapidly activated, which further aggravate the liver injury [1]. The ultimate consequence of this process is apoptotic or necrotic cell death, graft dysfunction, and graft loss [1]. From the findings of previous studies, it is now becoming clear that oxygen and its free radicals, called reactive...
oxygen species, play an important role in this process [5, 6].

Oxygen therapy was once regarded as a harmless treatment option [7]; however, several studies conducted in the field of critical care medicine have demonstrated that too much oxygenation could be harmful to the human body and that the restriction of oxygen supply would improve the outcomes of critically ill patients [8, 9]. Among patients admitted to the intensive care unit (ICU) following resuscitation of cardiac arrest, Kilgannon et al. showed that the first partial pressure of arterial oxygen (PaO\textsubscript{2}) after ICU admission equal to or more than 300 mmHg was independently associated with increased in-hospital mortality [10]. Therefore, avoiding excessive oxygen supply is now becoming a new standard for patients’ care [8].

Based on these findings, we hypothesized that excessive oxygen supply before and after graft reperfusion may influence the severity of IRI and the outcome after liver transplantation; however, this topic still remains unexplored. From the above, the aim of this study was to investigate the impact of higher intraoperative fraction of inspiratory oxygen (FiO\textsubscript{2}) on the outcome after living-donor-liver-transplantation (LDLT).

Patients and Methods

Study Design

A total of 219 adult (≥18 years old) patients underwent primary LDLT in Kyoto University Hospital from January 2010 through December 2017. Among them, patients with posterior segment graft (n = 8), who died within seven days of LDLT (n = 2) and with preoperative pulmonary complications (hepato-pulmonary syndrome and moderate to severe pulmonary hypertension or intrapulmonary arteriovenous shunt, n = 7) were excluded. In addition, patients with incomplete operation records (n = 3) were also excluded. Ultimately, 199 patients were enrolled in this study.

The donor–recipient selection criteria, detailed surgical procedure, and regimens of postoperative immunosuppression, including blood type incompatible liver transplantation, have been described previously [11–13]. In our institute, the anesthesiology team is responsible for the intraoperative circulatory and respiratory care of patients. Although the target of intraoperative FiO\textsubscript{2} was set at approximately 0.4, the anesthesiologists were free to control the FiO\textsubscript{2} at their discretion.

All study protocols were approved by the Ethics Committee of Kyoto University (Approval number: R1473–4), and all procedures were conducted in accordance with the Declaration of Helsinki of 1996.

Data Collection

Data were retrospectively collected from patient charts. The preoperative recipient demographic data collected were age, sex, status prior to surgery (hospitalized or ICU stay), etiology of liver disease, Model for End-stage Liver Disease (MELD) score, hepatorenal syndrome, percent vital capacity (%VC), forced expiratory volume in one second/forced vital capacity (FEV1/FVC ratio), and results of blood sample tests. The donor demographic data collected were age, graft-to-recipient weight ratio (GRWR), blood type–incompatible donor, and graft type. Intraoperative parameters included operation time, blood loss, cold and warm ischemia time, portal vein pressure (PVP), intraoperative splenectomy and total volume of infusion. Postoperative parameters included in-hospital mortality, result of blood culture, acute cellular and humoral rejection within one year after LDLT, early allograft dysfunction (EAD) rate, and causes of graft loss. Postoperative platelet count until postoperative day (POD) 42 and bilirubin level until POD 7 were also collected.

The intraoperative FiO\textsubscript{2} usually fluctuated during the operation; therefore, to precisely assess the difference of intraoperative FiO\textsubscript{2} between patients, the value was averaged using the total amount of intraoperative oxygen (O\textsubscript{2}) and air administered, i.e., the calculated FiO\textsubscript{2} (cFiO\textsubscript{2}) was defined as \( \{ \text{O}_2(L) + \text{Air}(L) \times 0.21 \}/(\text{O}_2(L) + \text{Air}(L)) \).

Recipients with %VC ≥80% and FEV1/FVC ratio ≥70% were classified as having normal pulmonary function. There were 23 cases of recipients (15 and 8 cases for cFiO\textsubscript{2} < 0.5 and ≥0.5 group, respectively) whose preoperative pulmonary functions were not measured due to the patient’s condition.

The results of arterial blood gas analyses including the PaO\textsubscript{2}, partial pressure of arterial carbon dioxide (PaCO\textsubscript{2}), HCO\textsubscript{3}–, and PaO\textsubscript{2}/FiO\textsubscript{2} (P/F) ratio were obtained at three time points during operation: at the start, within 30 min before or after portal reperfusion, and at the end of the operation.

Recipients’ preoperative skeletal muscle mass index (SMI), visceral to subcutaneous adipose tissue area ratio (VSR), and intra-muscular adipose tissue content (IMAC) were also collected, because our team previously reported that preoperative low SMI, high IMAC, and high VSR, i.e., “positive 3 body composition markers,” are independent risk factors for mortality after LDLT [14].

EAD was defined by the presence of one or more of the following: (i) total bilirubin ≥10 mg/dL on POD 7, (ii) prothrombin time-international normalized ratio ≥1.6 on POD 7, and (iii) aspartate aminotransferase or alanine aminotransferase ≥2000 IU/mL within the first seven postoperative days [15].
Parameters Analyzed

First, the distribution of cFiO₂ was evaluated and the factors associated with the difference of cFiO₂ between patients were assessed. Second, based on the previous study [16], patients were divided according to the cutoff value of the cFiO₂ “0.5.” Subsequently, the background and postoperative outcomes of patients were evaluated. Third, the prognostic factors associated with EAD were evaluated using univariable and multivariable analyses. The data included in the univariable analysis were determined according to the previous reports [17, 18]. Although the previous study has shown that a high preoperative bilirubin level is a risk factor for EAD [17], in this analysis, the clearance of total bilirubin level during the first seven days after LDLT, defined as “(preoperative bilirubin–POD7 bilirubin)/preoperative bilirubin,” was used instead of a simple preoperative bilirubin level. Finally, the postoperative survival curves of recipients with the cFiO₂ <0.5 and ≥0.5 were compared. Subsequently, the prognostic factors associated with overall graft survival were analyzed using univariable and multivariable analyses. The data included in the univariable analysis were also determined according to the previous reports [14, 19–23].

Statistical Analysis

Continuous data were expressed as the median and interquartile range (IQR) and were compared using the Wilcoxon rank-sum test. Categorical data were expressed as counts, and percentages and were compared using the Fisher’s exact test. The overall graft survival rate was calculated using the Kaplan–Meier method, and differences between curves were evaluated using the log-rank test. Variables with $P < 0.10$ in the univariable analysis were considered candidates for multivariable logistic regression analysis or Cox regression analysis. The results of the multivariable analysis are shown as odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CIs). According to the previous recommendation of the American Statistical Association [24], we avoided describing $P < 0.05$ as “statistically significant”; instead, we described the $P$ values as continuous quantities in the text, figures, and tables. All statistical analyses were performed using JMP Pro, version 14.0.0 (SAS Institute, Inc., Cary, NC).
A  P/F ratio at the start of the operation

B  P/F ratio at the start of the operation

C  Pulmonary function

D  Recipients' preoperative status

E  MELD score

F  PaO₂ at the start of the operation
Results

Distribution of cFiO₂ and the Factors Associated with the Variance

The cFiO₂ showed a bimodal distribution, and the peaks were found around 0.4 and 0.5 (Fig. 1); therefore, we evaluated the factors associated with the difference of the cFiO₂ between patients (Fig. 2). First, we divided the patients according to the P/F ratio at the start of the operation (Fig. 2A and B); however, both the P/F ratio ≥300 and ≥400 groups had a peak around cFiO₂ 0.5 and the P/F ratio <400 group also showed a peak around cFiO₂ 0.4. Patients were also divided according to their pulmonary function (Fig. 2C), recipients’ preoperative status (Fig. 2D), MELD score (Fig. 2E), and PaO₂ at the start of the operation (Fig. 2F); however, none seemed to influence the variance of cFiO₂. Finally, we also assessed the trend of the cFiO₂ during the observational period. As shown in Fig. 3, no apparent chronological changes in cFiO₂ were found during this observational period.

Summary of Patients’ Demographic Data (Table 1)

Recipients were divided into those with the cFiO₂ <0.5 (n = 156) and ≥0.5 (n = 43). Both groups showed almost comparable preoperative recipients’ background, donor factors, and intraoperative parameters. Although the P values of recipients’ preoperative alanine aminotransferase and intraoperative warm ischemia time were less than 0.05, the difference in actual values was almost clinically negligible. Postoperatively, the cFiO₂ ≥0.5 group showed a trend toward higher EAD rate than the cFiO₂ <0.5 group.

Figure 4 shows the results of arterial blood gas analyses during the operation. PaO₂ was first comparable between the two groups; however, the cFiO₂ ≥0.5 group showed higher PaO₂ during portal reperfusion and at the end of the operation compared to the cFiO₂ <0.5 group (Fig. 4A). The levels of PaCO₂ and HCO₃⁻ were almost similar between the two groups throughout the operation (Fig. 4B and C). The P/F ratio was first lower in the cFiO₂ ≥0.5 group; however, the values became almost comparable thereafter (Fig. 4D).

Comparisons of the postoperative platelet count and total bilirubin values are shown in Fig. 5. The cFiO₂ ≥0.5 group showed a trend toward lower platelet count after POD5 (Fig. 5A) and higher bilirubin levels after POD3 (Fig. 5B).
Table 1  Summary of patients’ characteristics

|                                | cFiO₂ <0.5 | cFiO₂ ≥0.5 | P  |
|--------------------------------|------------|------------|----|
|                                | n = 156    | n = 43     |    |
| Preoperative recipient factors  |            |            |    |
| Age, year*                      | 54 (46–61) | 53 (39–61) | 0.737 |
| Sex (male/female)               | 80/76      | 22/21      | 1.000 |
| Hospitalized or ICU, n (%)      | 84 (54)    | 26 (60)    | 0.491 |
| Positive 3 body composition markers, n (%) | 7 (5)  | 1 (2)     | 1.000 |
| Etiology                        |            |            | 0.324 |
| HBV/HCV, n (%)                  | 67 (43)    | 13 (30)    |    |
| AIH/PBC/PSC, n (%)              | 29 (19)    | 7 (16)     |    |
| Biliary atresia, n (%)          | 13 (8)     | 4 (9)      |    |
| Other, n (%)                    | 47 (30)    | 19 (44)    |    |
| Hepatocellular carcinoma, n (%) | 49 (31)    | 11 (26)    | 0.574 |
| Fulminant hepatic failure, n (%)| 5 (3)      | 3 (7)      | 0.375 |
| MELD score*                     | 17 (13–20) | 17 (13–27) | 0.468 |
| Hepatorenal syndrome, n (%)     | 11 (7)     | 6 (14)     | 0.213 |
| Respiratory function            |            |            |    |
| %VC, %*                         | 92 (78–104)| 86 (69–103)| 0.308 |
| FEV1/FVC ratio, %*              | 83.1 (78.7–87.6) | 83.4 (77.4–88.7) | 0.760 |
| Results of blood test           |            |            |    |
| AST, IU/L*                      | 53 (33–87) | 41 (27–67) | 0.052 |
| ALT, IU/L*                      | 32 (19–53) | 23 (17–35) | 0.023† |
| Albumin, g/dL*                  | 3.0 (2.4–3.2) | 3.0 (2.4–3.2) | 0.627 |
| Total bilirubin, mg/dL*         | 3.9 (2.0–8.3) | 3.3 (1.6–14.9) | 0.814 |
| Creatinine, mg/dL*              | 0.7 (0.6–0.9) | 0.7 (0.6–0.9) | 0.996 |
| PT-INR*                         | 1.5 (1.3–1.8) | 1.6 (1.3–1.9) | 0.440 |
| White blood cell count, × 1000/m³* | 3.7 (2.5–5.2) | 3.9 (2.7–5.9) | 0.582 |
| Hemoglobin, g/dL*               | 9.6 (8.5–11.5) | 9.2 (8.1–10.9) | 0.222 |
| Platelet count, × 1000/µL*      | 64 (39–101) | 66 (37–99) | 0.904 |
| Donor factors                   |            |            |    |
| Age, year*                      | 45 (31–56) | 45 (34–56) | 0.794 |
| GRWR, %*                        | 0.9 (0.7–1.1) | 0.8 (0.7–1.0) | 0.142 |
| Blood type incompatible donor, n (%) | 35 (22)  | 15 (34)   | 0.113 |
| Graft type, left/right lobe graft| 73/83     | 21/22      | 0.864 |
| Intraoperative parameters       |            |            |    |
| Operation time, hour*           | 14 (12–16) | 15 (12–18) | 0.421 |
| Blood loss, L*                  | 5.7 (3.5–10.2) | 6.8 (3.0–17.0) | 0.326 |
| Cold ischemia time, hour*       | 1.8 (1.0–2.8) | 2.2 (1.1–3.6) | 0.178 |
| Warm ischemia time, min*        | 44 (37–54) | 39 (33–50) | 0.012† |
| PVP before abdominal closure, mmHg* | 12 (10–14) | 13 (11–14) | 0.110 |
| Intraoperative splenectomy, n (%) | 65 (42)   | 13 (30)   | 0.217 |
| Total volume of infusion, L*     | 13.4 (9.9–18.3) | 14.8 (8.9–29.4) | 0.260 |
| Postoperative parameters        |            |            |    |
| In-hospital mortality, n (%)     | 20 (13)    | 8 (19)     | 0.330 |
| Positive blood culture, n (%)    | 49 (31)    | 20 (47)    | 0.072 |
| Reoperation, n (%)               | 29 (19)    | 14 (33)    | 0.060 |
| Acute cellular or humoral rejection, n (%) | 90 (58) | 25 (58) | 1.000 |
| EAD, n (%)                       | 50 (32)    | 21 (49)    | 0.049 |
| Causes of graft loss             |            |            | 0.684 |
Table 1 continued

|                               | $cFiO_2 < 0.5$ | $cFiO_2 \geq 0.5$ |
|-------------------------------|---------------|------------------|
| Liver failure, $n$ (%)        | 12 (35)       | 7 (44)           |
| Multiple organ failure, $n$ (%)| 7 (21)        | 2 (13)           |
| Sepsis, $n$ (%)               | 10 (29)       | 3 (19)           |
| ARDS, $n$ (%)                 | 1 (3)         | 0 (0)            |
| Other, $n$ (%)                | 4 (12)        | 4 (25)           |

$n = 156$, $n = 43$  

*Data are presented as the median and interquartile range. Calculated FiO$_2$ ($cFiO_2$) was defined as \( \{O_2(L) + Air(L) \times 0.21\}/(O_2(L) + Air(L)) \). *\( P < 0.05 \)

AIH autoimmune hepatitis; ALT alanine aminotransferase; ARDS acute respiratory distress syndrome; AST aspartate aminotransferase; EAD early allograft dysfunction; FEV1/FVC forced expiratory volume in one second/forced vital capacity; FiO$_2$ fraction of inspiratory oxygen; GRWR graft-to-recipient weight ratio; HBV hepatitis B virus; HCV hepatitis C virus; ICU intensive care unit; MELD model for end-stage liver disease; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis; PT-INR prothrombin time–international normalized ratio; PVP portal vein pressure; %VC percent vital capacity

**Fig. 4** The results of arterial blood gas analysis during operation. The $cFiO_2 \geq 0.5$ group showed higher PaO$_2$ at the portal reperfusion and at the end of the operation compared to the $cFiO_2 < 0.5$ group (A). The results of PaCO$_2$ (B) and HCO$_3^-$ (C) were almost similar between the two groups throughout the operation. The P/F ratio was initially lower in the $cFiO_2 \geq 0.5$ group; however, the value became almost comparable between the two groups during portal reperfusion (D). Calculated FiO$_2$ ($cFiO_2$) was defined as \( \{O_2(L) + Air(L) \times 0.21\}/(O_2(L) + Air(L)) \). FiO$_2$, fraction of inspiratory oxygen; PaCO$_2$, partial pressure of arterial carbon dioxide; PaO$_2$, partial pressure of arterial oxygen; P/F, PaO$_2$/FiO$_2$ ratio.
Risk Factor Analysis for EAD

Univariable analysis revealed that recipient age, gender, donor age, left lobe graft, and the \( \text{cFiO}_2 \geq 0.5 \) were potential risk factors for EAD after LDLT (Table 2). Multivariable analysis showed that the male recipients \( (P = 0.048) \) and donor age \( (P = 0.023) \) were independent risk factors for EAD. Although the \( P \) value did not reach the statistical threshold, the \( \text{cFiO}_2 \geq 0.5 \) was considered as a possible risk factor for EAD \( (P = 0.053) \).

Graft Survival After LDLT and Risk Factor Analysis

Figure 6 shows the overall graft survival after LDLT. The \( \text{cFiO}_2 \geq 0.5 \) group showed worse graft survival than the \( \text{cFiO}_2 < 0.5 \) group. Table 3 shows the results of the risk factor analysis for overall graft survival after LDLT. Univariable analysis revealed that the positive 3 body composition markers, donor age \( \geq 40 \) years, \( \text{GRWR} < 0.6\% \) blood type incompatible donor, and the \( \text{cFiO}_2 \geq 0.5 \) were potential risk factors for graft loss after LDLT. Multivariable analysis showed that the positive 3 body composition...
markers ($P < 0.001$), blood type incompatible donor ($P = 0.046$), and the $cFiO_2 \geq 0.5$ ($P = 0.048$) were independent risk factors for overall graft survival after LDLT.

### Discussion

The results of this study demonstrated that high intraoperative FiO$_2$ may be independently associated with worth graft outcome after LDLT. This is also confirmed by the fact that the $cFiO_2 \geq 0.5$ group showed higher EAD rate, although the $cFiO_2 \geq 0.5$ was not shown to be an independent factor in multivariable analysis.

In a previous experimental study, it was shown that perioperative hyperoxic conditions worsen liver IRI. Using a mouse partial liver ischemia–reperfusion model, Zangl et al. demonstrated that the mice under postoperative hyperoxic (FiO$_2 = 0.6$) conditions showed higher glutamate-pyruvate-transaminase level, reactive oxygen species, and histological injury score than the mice under normoxic (FiO$_2 = 0.21$) conditions [25]. Subsequently, they showed that the harmful effects of high FiO$_2$ were ameliorated by depletion of granulocytes or Kupffer cells or by knocking out the p47phox unit of the NADPH-oxidase [25]. Considering that granulocytes and Kupffer cells are the main sources of reactive oxygen species, their results suggested that oxygen is a very important factor that affects IRI and that restriction of oxygen supply may decrease the severity of liver injury after ischemia–reperfusion.

In our study, the $cFiO_2 \geq 0.5$ groups showed a worse overall graft survival after LDLT. Regarding short-term outcomes, the $cFiO_2 \geq 0.5$ group was also associated with a higher rate of EAD. Univariable analysis showed that higher $cFiO_2$ was a potential risk factor for EAD; however, it did not reach the statistical threshold for independent risk

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**Table 2** Univariable and multivariable analyses for factors associated with EAD

|                        | Univariable analysis |                         | Multivariable analysis |                          |
|------------------------|----------------------|-------------------------|------------------------|-------------------------|
|                        | OR 95%CI             | $P$                     | OR 95%CI               | $P$                     |
| **Recipient preoperative factors** |                      |                         |                        |                         |
| Recipient age, per 10 years* | 0.803 0.638–1.011 | 0.061                   | 0.824 0.650–1.046     | 0.112                   |
| Recipient sex, male     | 0.434 0.239–0.786    | 0.006                   | 0.510 0.261–0.996     | 0.048                   |
| Fulminant hepatic failure | 3.205 0.743–13.834   | 0.119                   |                        |                         |
| AST, per 1 IU/L*        | 0.999 0.995–1.004    | 0.925                   |                        |                         |
| ALT, per 1 IU/L*        | 0.998 0.992–1.004    | 0.429                   |                        |                         |
| Total-bilirubin clearance* $\xi$ | 0.936 0.824–1.063 | 0.312                   |                        |                         |
| Albumin, g/dL*          | 0.875 0.537–1.427    | 0.593                   |                        |                         |
| Creatinine, mg/dL*      | 1.138 0.823–1.574    | 0.432                   |                        |                         |
| Hepatorenal syndrome    | 1.692 0.622–4.602    | 0.303                   |                        |                         |
| **Donor factors**       |                      |                         |                        |                         |
| Donor age, per 5 year*  | 1.116 0.999–1.247    | 0.049                   | 1.146 1.016–1.292     | 0.023                   |
| GRWR, per 0.1%*         | 0.898 0.783–1.030    | 0.120                   |                        |                         |
| Blood type incompatible donor | 0.804 0.407–1.589 | 0.531                   |                        |                         |
| Left lobe graft         | 1.934 1.074–3.481    | 0.028                   | 1.740 0.880–3.441     | 0.112                   |
| **Intraoperative parameters** |                      |                         |                        |                         |
| Blood loss, per 1L*     | 0.992 0.954–1.031    | 0.669                   |                        |                         |
| Cold ischemia time, per 1 h* | 0.848 0.681–1.055 | 0.119                   |                        |                         |
| P/F ratio at the start of operation <300 | 0.703 0.380–1.303 | 0.263                   |                        |                         |
| P/F ratio at the start of operation <400 | 1.104 0.613–1.991 | 0.740                   |                        |                         |
| $cFiO_2 \geq 0.5$       | 2.024 1.020–4.018    | 0.044                   | 2.038 0.992–4.186     | 0.053                   |
| Final PVP $\geq 15$ mmHg | 0.897 0.393–2.044    | 0.794                   |                        |                         |

*The factor is included in the analysis as continuous data. Calculated FiO$_2$ ($cFiO_2$) was defined as $\{O_2(L) \times Air(L) \times 0.21\}/\{O_2(L) + Air(L)\}$. †$P < 0.05$ on multivariate analysis. $\xi$ The formula for total bilirubin clearance is as follows: (preoperative bilirubin–POD7 bilirubin)/preoperative bilirubin

ALT alanine aminotransferase; AST aspartate aminotransferase; CI confidence interval; EAD early allograft dysfunction; FiO$_2$ fraction of inspiratory oxygen; GRWR graft-to-recipient weight ratio; OR odds ratio; P/F PaO$_2$/FiO$_2$ ratio; PVP portal vein pressure
factor in multivariable analysis. This may be because the difference in cFiO₂ between the two groups (median 0.44 for the cFiO₂ <0.5 group and 0.53 for the cFiO₂ ≥0.5 group, respectively) was not strong enough to detect the difference in the EAD rate. If we could have compared the FiO₂ 0.3 and 0.8, which were used in several prospective studies [26–28], the difference in short-term outcomes might have appeared more clearly. Liver transplantation is a life-saving procedure, and recipients are usually critically ill; therefore, it would be ethically difficult to conduct a prospective study allocating patients into extremely different intraoperative FiO₂. We think the results of this study suggested the possibility that high intraoperative FiO₂ might increase the EAD rate and could lead to worse graft outcomes after LDLT.

A lower P/F ratio at the start of the operation would be the main reason for the higher oxygen supply in the cFiO₂ ≥0.5 group (Fig. 4D). However, in the cFiO₂ ≥0.5 group, the P/F ratio improved thereafter and the PaO₂ increased during portal reperfusion than in the cFiO₂ <0.5 group (Fig. 4A). Resolving of atelectasis by positive

Table 3 Univariable and multivariable analyses for factors associated with overall graft survival

| Recipient preoperative factors | Univariable analysis | Multivariable analysis |
|-------------------------------|----------------------|------------------------|
|                               | HR   | 95%CI   | P    | HR   | 95%CI   | P    |
| Recipient age, per 10 years*  | 1.041 | 0.839–1.313 | 0.723 | 6.883 | 2.704–15.374 | <0.001† |
| Recipient sex, male           | 0.628 | 0.354–1.097 | 0.103 | 1.403 | 0.767–2.681 | 0.277 |
| Positive 3 body composition marker | 7.232 | 2.918–15.503 | <0.001 | 1.013 | 0.414–2.129 | 0.976 |
| Fulminant hepatic failure     | 1.783 | 0.433–4.864 | 0.371 | 1.013 | 0.414–2.129 | 0.976 |
| MELD, per 1 score*            | 1.023 | 0.990–1.054 | 0.168 | 1.023 | 0.990–1.054 | 0.168 |
| AST, per 1 IU/L*              | 0.999 | 0.994–1.003 | 0.762 | 0.999 | 0.994–1.003 | 0.762 |
| ALT, per 1 IU/L*              | 0.999 | 0.993–1.003 | 0.845 | 0.999 | 0.993–1.003 | 0.845 |
| Total bilirubin, mg/dL*       | 1.008 | 0.976–1.034 | 0.612 | 1.008 | 0.976–1.034 | 0.612 |
| Albumin, g/dL*                | 1.276 | 0.807–2.006 | 0.296 | 1.276 | 0.807–2.006 | 0.296 |
| Creatinine, mg/dL*            | 1.135 | 0.866–1.351 | 0.303 | 1.135 | 0.866–1.351 | 0.303 |

| Donor factors                 |                    |                        |           |
| Donor age ≥40 years           | 1.704 | 0.949–3.214 | 0.075 | 1.403 | 0.767–2.681 | 0.277 |
| GRWR <0.6%                    | 2.609 | 0.903–5.982 | 0.073 | 2.016 | 0.694–4.666 | 0.178 |
| Blood type incompatible donor | 2.007 | 1.114–3.523 | 0.021 | 1.854 | 1.012–3.297 | 0.046† |

| Intraoperative parameters     |                    |                        |           |
| Blood loss, per 1L*           | 0.992 | 0.949–1.008 | 0.672 | 0.992 | 0.949–1.008 | 0.672 |
| Cold ischemia time, per 1 h*  | 0.937 | 0.752–1.119 | 0.508 | 0.937 | 0.752–1.119 | 0.508 |
| P/F ratio at the start of operation <300 | 1.068 | 0.595–2.015 | 0.830 | 1.068 | 0.595–2.015 | 0.830 |
| P/F ratio at the start of operation <400 | 1.031 | 0.581–1.799 | 0.581 | 1.031 | 0.581–1.799 | 0.581 |
| cFiO₂ ≥0.5                   | 1.868 | 1.004–3.331 | 0.047 | 1.897 | 1.007–3.432 | 0.048† |
| Final PVP ≥15 mmHg           | 1.013 | 0.414–2.129 | 0.976 | 1.013 | 0.414–2.129 | 0.976 |

*The factor is included in the analysis as continuous data. Calculated FiO₂ (cFiO₂) was defined as {O₂(L) + Air(L) × 0.21}/(O₂(L) + Air(L)). † P <0.05 on multivariate analysis. ALT alanine aminotransferase; AST aspartate aminotransferase; CI confidence interval; EAD early allograft dysfunction; FiO₂ fraction of inspiratory oxygen; GRWR graft-to-recipient weight ratio; HR hazard ratio; MELD model for end-stage liver disease; P/F PaO₂/FiO₂ ratio; PVP portal vein pressure.
pressure ventilation or removal of a large amount of ascites or pleural effusion may be associated with improved oxygenation in the cFiO2 ≥0.5 group. As shown in the Supplementary Figure, spot FiO2 was gradually decreased during operation even in the cFiO2 ≥0.5 group; however, the difference was smaller than that observed in the cFiO2 <0.5 group; therefore, the FiO2 became relatively higher than expected, and the liver grafts were exposed to a higher oxygen environment in the cFiO2 ≥0.5 group. These results suggest that intraoperative FiO2 can be reduced safely in some patients, which may lead to the suppression of IRI, lower EAD rate, and improved outcome after LDLT.

Our study has several limitations. First, the study was retrospective and conducted in a single institution. Our results should be confirmed in multicenter prospective studies. Second, it would have been more informative if we could have assessed all possible parameters in our institute during risk factor analysis for EAD and graft survival. However, due to the limited number of patients, we selected the factors included in the analysis, according to the results of previous studies. Further accumulation of cases is needed for a more accurate investigation. Last, we have to be careful about applying the results of this study to the patients undergoing LDLT. We think that these results do not mean the intraoperative FiO2 should be kept “lower as possible.” Intraoperative FiO2 should be adjusted according to the condition of each patient and critically ill patients sometimes need higher than usual oxygen to maintain a normal oxygenation level. However, as is shown in this study, even the most of the patients in cFiO2 <0.5 group showed PaO2 over 120 mmHg and those in cFiO2 >0.5 group showed further higher PaO2 during LDLT; therefore, we think that FiO2 could be reduced safely for these patients. From the above, we think that our results should be interpreted as “avoiding unnecessarily high intraoperative FiO2 in LDLT.”

In conclusion, this retrospective study suggested that intraoperative high FiO2 might increase EAD and have some impact on graft survival after LDLT. Avoiding unnecessarily high intraoperative oxygenation may have some beneficial effects in patients undergoing LDLT.

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Declarations

Conflict of interest All authors declared no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Ethical Approval All study protocols were approved by the Ethics Committee of Kyoto University (Approval number: R1473-4), and all procedures were conducted in accordance with the Declaration of Helsinki of 1996.

References

1. Abu-Amara M, Yang SY, Tapuria N et al (2010) Liver ischemia/ reperfusion injury: processes in inflammatory networks—a review. Liver Transpl 16:1016–1032
2. Churchill TA, Cheetham KM, Fuller BJ et al (1994) Glycolysis and energy metabolism in rat liver during warm and cold ischemia: evidence of an activation of the regulatory enzyme phosphofructokinase. Cryobiology 31:441–452
3. Kurokawa T, Kobayashi H, Nonami T et al (1996) Mitochondrial glutathione redox and energy producing function during liver ischemia and reperfusion. J Surg Res 66:1–5
4. Fukai M, Hayashi T, Yokota R et al (2005) Lipid peroxidation during ischemia depends on ischemia time in warm ischemia and reperfusion of rat liver. Free Radic Biol Med 38:1372–1381
5. Wu MY, Yang GT, Liao WT et al (2018) Current mechanistic concepts in ischemia and reperfusion injury. Cell Physiol Biochem 46:1650–1667
6. Jaeschke H, Smith CV, Mitchell JR (1988) Reactive oxygen species during ischemia-reflow injury in isolated perfused rat liver. J Clin Invest 81:1240–1246
7. Habre W, Petak F (2014) Perioperative use of oxygen: variabilities across age. Br J Anaesth 113(Suppl 2):ii26–ii36
8. O’Driscoll BR, Howard LS, Davison AG (2008) BTS guideline for emergency oxygen use in adult patients. Thorax 63(Suppl 6):vi1–vi68
9. Six S, Jaffal K, Ledoux G et al (2016) Hyperoxemia as a risk factor for ventilator-associated pneumonia. Crit Care 20:195
10. Kilgannon JH, Jones AE, Shapiro NI et al (2010) Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA 303:2165–2171
11. Tanaka K, Ogura Y, Kiuchi T et al (2004) Living donor liver transplantation: eastern experiences. HPB 6:88–94
12. Morikawa D, Egawa H, Kasahara M et al (2007) Outcomes of adult-to-adult living donor liver transplantation: a single institution’s experience with 333 consecutive cases. Ann Surg 245:315–325
13. Kaido T, Ogawa K, Fujimoto Y et al (2013) Impact of sarcopenia on survival in patients undergoing living donor liver transplantation. Am J Transplant 13:1549–1556
14. Hamaguchi Y, Kaido T, Okumura S et al (2018) Proposal for new selection criteria considering pre-transplant muscularity and visceral adiposity in living donor liver transplantation. J Cachexia Sarcopenia Muscle 9:246–254
15. Wadei HM, Lee DD, Croome KP et al (2016) Early allograft dysfunction after liver transplantation is associated with short- and long-term kidney function impairment. Am J Transplant 16:850–859
16. Hovaguimian F, Lysakowski C, Elia N et al (2013) Effect of intraoperative high inspired oxygen fraction on surgical site infection, postoperative nausea and vomiting, and pulmonary function: systematic review and meta-analysis of randomized controlled trials. Anesthesiology 119:303–316
17. Pomposelli JJ, Goodrich NP, Emond JC et al (2016) Patterns of early allograft dysfunction in adult live donor liver transplantation: the A2ALL experience. Transplantation 100:1490–1499
18. Song JL, Yang J, Yan LN et al (2017) A new index predicts early allograft dysfunction following living donor liver transplantation: a propensity score analysis. Dig Liver Dis 49:1225–1232
19. Uemura T, Wada S, Kaido T et al (2016) How far can we lower graft-to-recipient weight ratio for living donor liver transplantation under modulation of portal venous pressure? Surgery 159:1623–1630
20. Kubota T, Hata K, Sozu T et al (2018) Impact of donor age on recipient survival in adult-to-adult living-donor liver transplantation. Ann Surg 267:1126–1133
21. Yao S, Kaido T, Uozumi R et al (2018) Is portal venous pressure modulation still indicated for all recipients in living donor liver transplantation? Liver Transpl 24:1578–1588
22. Yao S, Kaido T, Yagi S et al (2019) Impact of imbalanced graft-to-spleen volume ratio on outcomes following living donor liver transplantation in an era when simultaneous splenectomy is not typically indicated. Am J Transplant 19:2783–2794
23. Kamo N, Kaido T, Hammad A et al (2015) Impact of elderly donors for liver transplantation: a single-center experience. Liver Transpl 21:591–598
24. Wasserstein RL, Lazar NA (2016) The ASA statement on p-values: context, process, and purpose. Am Stat 70:129–133
25. Zangl Q, Martignoni A, Jackson SH et al (2014) Postoperative hyperoxia (60%) worsens hepatic injury in mice. Anesthesiology 121:1217–1225
26. Belda FJ, Aguilera L, García de la Asunción J et al (2005) Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. JAMA 294:2035–2042
27. Bickel A, Gurevits M, Vamos R et al (2011) Perioperative hyperoxygenation and wound site infection following surgery for acute appendicitis: a randomized, prospective, controlled trial. Arch Surg 146:464–470
28. García-Botello SA, García-Granero E, Lillo R et al (2006) Randomized clinical trial to evaluate the effects of perioperative supplemental oxygen administration on the colorectal anastomosis. Br J Surg 93:698–706

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