Original Article

Anesthesia management for lung transplant in children with obliterated bronchiolitis after hematopoietic stem cell transplantation: a single-center experience

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Background: Lung transplantation (LTx) is the definitive treatment for patients with end-stage lung diseases, but its application in pediatrics is limited by donor scarcity and surgical complexity. There is a general lack of experience and consensus on anesthetic management during LTx in children with bronchiolitis obliterans syndrome (BOS). We summarized the data of children undergoing LTx with BOS after hematopoietic stem cell transplantation (HSCT) at The Second Affiliated Hospital of Zhejiang University School of Medicine (SAHZU) to devise an anesthetic management strategy and describe practical experience.

Methods: Children with BOS who underwent LTx at SAHZU from January 2021 to September 2023 were reviewed. Data on demographics, perioperative clinical parameters, and outcomes were collected and recorded. Transesophageal echocardiography (TEE) guided the dynamic evaluation of cardiac function, volume management, and pulmonary vascular anastomosis. Pulmonary artery catheters (PACs) were used to monitor pulmonary artery pressure (PAP).

Results: Ten children with BOS post-HSCT underwent LTx, including eight males and two females. One patient had a single LTx, and the others had double LTx. All children received allogeneic red blood cell (RBC) infusion. Three received continuous renal replacement therapy (CRRT) during the operation. Postoperative mechanical ventilation time was 2 (IQR, 2–24) days. Extracorporeal membrane oxygenation (ECMO) time was 12 (IQR, 6–12) hours. Four patients developed acute kidney injury (AKI) within 48 hours, and primary graft dysfunction grade 3 (PGD3) occurred in 10% within 48–72 hours. Intensive care unit (ICU) stay was 9 (IQR, 6–40) days, and the 30-day survival rate was 100%.

Conclusions: Preoperative evaluation, volume management, hemodynamic monitoring, TEE, and ECMO application are the key points that anesthesiologists should pay attention to in such cases.

Keywords: Bronchiolitis obliterans syndrome (BOS); lung transplantation (LTx); transesophageal echocardiography (TEE); extracorporeal membrane oxygenation (ECMO)

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Introduction

Lung transplantation (LTx) is the last resort of treatment for patients with end-stage lung diseases, including idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF). According to the International Society for Heart and Lung Transplantation (ISHLT), more than 67,000 patients underwent LTx between January 1992 and June 2018 (1). Over the past few decades, COPD has emerged as the most common indication of LTx worldwide (2). In recent years, the number of patients undergoing LTx for interstitial lung disease (ILD) has gradually increased. Unlike cases of adult LTx, medical centers that can independently perform pediatric LTx are scant due to the scarcity of donors and technical difficulties. Since the first LTx was performed on a child with familial pulmonary fibrosis at the University of Toronto in Canada in 1987 (3), this revolutionary technology has benefited several children with end-stage lung disease. From January 2010 to June 2018, 970 pediatric LTx cases were registered in the ISHLT database (4). CF is the most common indication for pediatric LTx, followed by pulmonary vascular disease (PVD) (5,6). Bronchiolitis obliterans syndrome (BOS) after hematopoietic stem cell transplantation (HSCT) is uncommon in the United States. However, in China, BOS after HSCT has emerged as the main indication for pediatric LTx. This difference in primary indications may reflect regional variations in patient populations and healthcare practices.

BOS is a pulmonary manifestation of graft-versus-host disease (GVHD) because airflow obstruction and reduced lung function are observed in GVHD after transplantation of other organ transplants (7). Scarring, stenosis, and obstruction of small airways are important causes of progressive deterioration or even loss of pulmonary function in children with BOS (8). Although BOS is uncommon after HSCT, it severely limits patients' daily activities and reduces their quality of life (9,10). It remains the main cause of late death after HSCT. Because existing diagnostic criteria may not capture early asymptomatic airflow limitation, reduced forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) is likely to reflect the advanced stages of the disease (7), at which time LTx remains the last option for these patients.

High oxygen dependence, nutrition, and complications (including pulmonary infection and cardiac insufficiency) in children with BOS make the management of anesthesia challenging. At present, there is no documented literature of anesthesia management in pediatric LTx cases with BOS. In this study, we summarize the clinical data of children with BOS who underwent LTx at The Second Affiliated Hospital of Zhejiang University School of Medicine (SAHZU) to draw inferences from our experience at this stage. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2024-2273/rc).

Highlight box

Key findings

- In 10 children with bronchiolitis obliterans syndrome (BOS) after hematopoietic stem cell transplantation (HSCT) undergoing lung transplantation (LTx), an anesthetic protocol integrating transesophageal echocardiography (TEE), pulmonary artery catheter (PAC), and pulse indicator continuous cardiac output (PiCCO) monitoring alongside restrictive fluid management and tailored extracorporeal membrane oxygenation (ECMO) support achieved 100% 30-day survival.
- Median intraoperative red blood cell transfusion was 18 mL/kg; acute kidney injury occurred in 40% and primary graft dysfunction grade 3 in 10%.
- Central veno-arterial ECMO was employed in 60% of cases to maintain hemodynamic stability during reperfusion and anastomosis.

What is known and what is new?

- Pediatric LTx for BOS post-HSCT is rare, with high perioperative risk and no consensus on anesthesia management.
- This study introduces a comprehensive approach combining advanced hemodynamic monitoring (TEE, PAC, PiCCO), low tidal volume ventilation, restrictive fluid strategies guided by real-time metrics, and proactive ECMO deployment. We demonstrate the feasibility and safety of this integrated protocol, with favorable early postoperative outcomes.

What is the implication, and what should change now?

- Implementation of multidisciplinary preoperative assessment and standardized intraoperative monitoring protocols may reduce complications and optimize resource utilization in pediatric LTx for BOS.
- Future clinical guidelines should incorporate these evidence-based strategies to improve perioperative care and long-term outcomes.

Methods

Patients and indication

Clinical data of all children with BOS who underwent LTx at SAHZU between January 2021 and September 2023 were retrospectively collected and described.

At SAHZU, children with an expected survival time of less than 2 years and no signs of relapse for at least 1 year after HSCT and genetic testing are candidate recipients for a lung transplant. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Human Body Research Ethics Committee of The Second Affiliated Hospital of Zhejiang University School of Medicine (No. 2022-0352). The requirement for written informed consent was waived because of the retrospective observational design of the study.

Selection of donors

At SAHZU, suitable donors should meet the following criteria: age <18 years; no history of chronic lung disease; matching of ABO blood group and donor-recipient size; no specific pathogenic microorganisms detected in culture; arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≥300 mmHg; positive end-expiratory pressure (PEEP) <5 cmH_2O; chest X-ray showing no extensive infiltration, and no pneumothorax or trauma.

Multidisciplinary team (MDT) and preoperative assessment

For all children with BOS, we recommend participation in multi-rounds of MDT discussions, including the department of LTx, anesthesiology, intensive care unit (ICU), pediatrics, nutrition, rehabilitation, and hematology.

All children with BOS at SAHZU must undergo comprehensive evaluation (including nutrition, cardiopulmonary function, airway assessment, and psychological state) in a stable period after HSCT to choose the best operation time.

Preparation before anesthesia

Preparation for anesthesia should begin at least one hour before entering the room, and no additional drugs should be administered to the children before the operation. Instruments required include cerebral oxygen saturation (ScO_2) monitor, cardiac output (CO) monitor, transesophageal echocardiography (TEE), autologous blood recovery, endotracheal or double-lumen bronchial catheter, video laryngoscope, fiberoptic bronchoscope (FOB), and hotline fluid warmer. Vasoactive drugs, such as norepinephrine, epinephrine, milrinone, dobutamine, and vasopressin, should be prepared.

Children arrived at the operating room and were administered oxygen ≥5 L/min, while others who were in the state of tracheal intubation or tracheotomy received immediate mechanical ventilation. Monitoring immediately after arriving in the operating room included assessing non-invasive arterial blood pressure, 5-lead electrocardiogram (ECG), arterial oxygen saturation (SaO_2), bispectral index (BIS), and ScO_2. An ultrasound-guided radial artery catheterization and left central venous catheterization were completed in children, showing good coordination promptly before induction. The thermoregulatory center is suppressed during general anesthesia in children, and exposure to a wide range of wounds can easily lead to heat loss. Therefore, we used a water temperature blanket and hotline fluid warmer to maintain the body temperature.

Anesthetic management

Induction and maintenance of anesthesia

Anesthesia was induced in all children following a standardized regimen, which included the administration of propofol (1.5–2.5 mg/kg), midazolam (0.05–0.1 mg/kg), fentanyl (4–6 μg/kg), or sufentanil (0.5–1 μg/kg), and rocuronium bromide (0.6–0.9 mg/kg) or cisatracurium (0.1–0.3 mg/kg). All patients underwent lung isolation techniques. Selection of a double-lumen bronchial catheter, bronchial blocker, or single-lumen endobronchial tube was based on the estimated internal airway diameter measured by computed tomography (CT). The transesophageal ultrasound probe was placed after ensuring effective alignment of the catheter.

Anesthesia was maintained using an intravenous and inhalation combination approach, with propofol (9–15 mg/kg/h), sufentanil (1–2 μg/kg/h), cisatracurium (0.06–0.12 mg/kg/h), while maintaining the sevoflurane inhalation concentration at 0–2 %. The depth of anesthesia was adjusted based on the continuous monitoring of the electroencephalogram BIS (Covidien LLC, Mansfield, MA, USA).

Intraoperative monitoring

Routine monitoring [electrocardiographic monitoring, oxygen saturation, and non-invasive blood pressure (non-IBP)] was performed after entering the operating room. IBP monitoring and peripheral venous access were rapidly established. An ultrasound-guided central venous catheter (B. Braun Melsungen AG, Melsungen, Germany) was

inserted into the left internal jugular vein to establish access to the central venous and measure the central venous pressure (CVP). The central venous catheter was inserted into the right jugular vein, and pulmonary artery catheter (PAC) (Bioptimal International Pte. Ltd., Singapore, Singapore) was performed.

Baseline values of ScO_2 and BIS were determined before anesthesia induction. Placing the esophageal ultrasound probe after left internal jugular vein puncture is recommended, and a preliminary assessment before extracorporeal life support (ECLS) should be performed. TEE can guide extracorporeal membrane oxygenation (ECMO) sheath placement and is used to dynamically assess cardiac function (ejection fraction (EF), tricuspid annular plane systolic excursion (TAPSE), and vascular anastomosis (pulmonary artery flow rate, pulmonary vein flow rate, and anastomotic diameter). Pulmonary artery occlusion and pulmonary vascular opening are critical time points during LTx but TEE assessment should not be limited by this. Pulse indicator continuous CO (PiCCO) technology is an efficient and advanced system for monitoring the hemodynamic status of patients. The continuous hemodynamic monitoring with PiCCO was achieved via the insertion of large arterial catheters and central venous catheters. CVP, pulmonary artery pressure (PAP), CO, cardiac index (CI), systemic vascular resistance (SVR), and stroke volume variation (SVV) and other hemodynamic data were measured by the PiCCO thermodilution. At SAHZU, we use a smaller size PAC and a matching sheath, and all children undergoing LTx have the PAC placed under the guidance of the sheath.

Mechanical ventilation

For bilateral lung ventilation, the initial setting is recommended to be low tidal volume (VT), approximately 6–8 mL/kg. During single-lung ventilation, lung-protective strategies such as pressure-controlled ventilation-volume guaranteed (PCV-VG) are preferred, with a recommended VT of 4–6 mL/kg. Before reventilating the graft, it is necessary to check bronchial anastomosis using a FOB to exclude any causes of anastomotic stenosis and bleeding. Manual lung inflation was performed after secretions and blood were fully aspirated. After reperfusion, to alleviate ischemia-reperfusion injury of the graft, a lung-protective ventilation strategy with low oxygen concentration, high PEEP, and low VT should be employed. We recommend setting PEEP at 6–10 cmH_2O, peak airway pressure <30 cmH_2O, adjusting FiO_2 to less than 30–40% while maintaining PaO_2 ≥70 mmHg, and maintaining end-tidal carbon dioxide ($P_{ET}CO_2$) within the normal range or acceptable hypercapnia levels. Increasing the inspired oxygen concentration after reperfusion is not recommended unless oxygen saturation becomes difficult to maintain under one-lung ventilation. Blood gas analysis can guide the adjustment of ventilator parameters to prevent hypercapnia and reperfusion injury.

Volume management

Strict restrictive fluid therapy can minimize pulmonary edema and reduce the incidence of primary graft dysfunction (PGD), so the application of restrictive volume management strategies in pediatric LTx is recommended. However, incorporating restrictive fluid therapy strategies throughout LTx surgery can lead to clinical challenges, such as hypoperfusion of kidneys, unnecessary use of vasoactive drugs, arrhythmia, and circulatory collapse, which may be induced under low-volume conditions. Therefore, evaluating systemic blood volume under TEE and CVP guidance is advised while not completely ignoring basal fluid requirements in fluid therapy strategies. However, after graft reperfusion, the fluid infusion should be strictly limited and the use of high-concentration albumin and diuretics to keep the graft in a "dry" state is strongly recommended. The intraoperative infusion volume of crystalline fluid should be strictly limited. In patients with BOS, sodium acetate Ringer's solution and physiological saline were chosen. Although lactate Ringer's solution is widely used in LTx surgery in other centers, considering the potential risk of increased metabolic acidosis, it was not the preferred crystalline solution. An artificial colloidal solution is not recommended. Targeted liquid therapy has limitations in guiding volume management during LTx because the set goals are difficult to unify and standardize, and after bridging with ECLS, it interferes with many monitoring targets. There is no clear documented literature to prove the advantages of targeted liquid therapy in LTx volume management.

TEE

After completing anesthesia induction, the esophageal ultrasound probe was inserted. In patients with BOS undergoing LTx, TEE focuses on guiding the placement of ECMO sheaths, checking pulmonary vascular anastomosis, evaluating cardiac function dynamically, and guiding intraoperative volume management. Veno-venous ECMO (VV-ECMO) can provide respiratory support for children

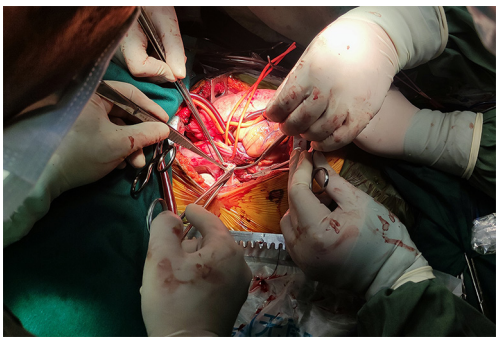

Figure 1 Central VA-ECMO on pediatric LTx. LTx, lung transplantation; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

undergoing LTx, and it involves the implementation of two catheters for femoral vein drainage catheterization and internal jugular vein catheterization. Internal medicine doctors usually roughly estimate the depth of catheter placement based on the height of the patient but non-visual methods limit intubation's accuracy. Due to thinner blood vessels and smaller ventricular size in children, the potential risk of catheter misalignment may be higher. Catheter misalignment has serious consequences, including insufficient ECMO flow, hypoperfusion, hypoxia, and vascular damage. Therefore, the ECMO catheters should be placed under TEE guidance.

In cases of anastomotic complications in the pulmonary artery, blood flow into the allograft lung is hindered, which increases the right ventricular afterload, leading to right heart dysfunction, hypoxemia, and PGD. After opening up the pulmonary artery, TEE is recommended to evaluate pulmonary artery flow velocity. If the average peak velocity of pulmonary artery is greater than 2 m/s, caution should be exercised for pulmonary artery obstruction. Pulmonary vein anastomotic obstruction may occur due to allograft torsion, mismatch between donor lung and thoracic cavity, and anastomotic stenosis or thrombosis. Our experience suggests that pulmonary vein flow velocity >100 cm/s indicates possible obstruction. Color Doppler flow can provide additional documented literature.

Perioperative management in children with combined pulmonary hypertension or cardiac dysfunction in addition to BOS is challenging, especially after pulmonary artery clamping, which may significantly increase right ventricular afterload and cause acute failure of the right heart.

Timely stabilization of the function of the right heart can reduce the incidence of adverse reactions and improve patient prognosis. PAC and TEE are undoubtedly the best methods of monitoring PAP and right heart function dynamically. Briefly, ventricular size, TAPSE, and interventricular septal morphology can be used to quickly evaluate right heart function and guide positive inotropic drug and fluid therapy during surgery. Anesthesiologists should use TEE to assess the function of the right heart immediately after the following situations: (I) when PAP rapidly increases after clamping pulmonary artery; (II) the heart rate increases rapidly in a short period, accompanied by hemodynamic instability; (III) the right heart is plump under direct vision; and (IV) in cases of malignant arrhythmias (such as supraventricular tachycardia, and RR long intervals).

Timing of transfer to veno-arterial ECMO (VA-ECMO) and conditions for ECMO withdrawal

The timing of VV-ECMO to VA-ECMO is a focus of clinical attention, especially in cases of pediatric LTx, where sufficient documented literature is lacking. However, it is rare for children with BOS to have moderate to severe pulmonary hypertension. We evaluated the timing of cardiac support based on cardiac function. If TEE indicated a significant enlargement of the right ventricle, the ventricular septum was compressed, along with signs of circulatory failure. VA-ECMO support was considered. Considering that younger children have thinner peripheral blood vessels, central VA-ECMO support is a more common choice (*Figure 1*).

At SAHZU, patients who receive VV-ECMO intraoperatively do not have the ECMO withdrawn immediately after LTx. The purpose of this way is to maintain oxygenation for a certain period and reduce ventilator support. All pediatric patients who receive central VA-ECMO support intraoperatively have the ECMO withdrawn postoperatively. Cardiopulmonary function should be evaluated before the withdrawal of central VA-ECMO. The withdrawal of ECMO should be guided by the dynamic monitoring results of PAP and right heart function by PAC and TEE. When the ECMO flow was gradually reduced to 1/4–1/3 of the previous flow, no additional vasoactive drugs are needed, and hemodynamics are stable, ECMO withdrawal is considered relatively safe. Diuretic use before reperfusion is necessary to avoid increasing the risk of potential pulmonary edema. In children who develop pulmonary edema with increased airway pressure or volume overload immediately after reperfusion, timely use of continuous renal replacement

Table 1 Demographic and general characteristics of child patients

Variables	Data (n=10)
Age (years)	11 [8–15]
Gender	
Male	8 [80]
Female	2 [20]
Height (cm)	133 [118–143]
Weight (kg)	23 [14–38]
BMI (kg/m^2)	15.58 [11.38–18.68]
Blood group	
A+	5 [50]
B+	0 [0]
AB+	1 [10]
O+	4 [40]
ASA grade	
IV	9 [90]
V	1 [10]
Surgical type	
Single LTx	1 [10]
Double LTx	9 [90]
Preoperative ECMO	
No	10 [100]
Yes	0 [0]
Preoperative tracheal intubation	
No	8 [80]
Yes	2 [20]
PAP (mmHg)	30.0 [25.5–34.25]
Lung function parameters	
FEV1 (L)	1.5 [1.1–2.4]
FEV1%	23.1 [16.7–44.1]
FVC (L)	0.67 [0.53–1.78]
FVC%	42.8 [38.0–61.5]
FEV1/FVC	41.14 [31.49–69.83]

Data are presented as n [%] or median [IQR]. ASA, American Society of Anesthesiologists; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; LTx, lung transplantation; PAP, pulmonary artery pressure.

therapy (CRRT) is recommended but hemodynamics must be closely monitored, and the dosage of vasoactive drugs must be adjusted. Caution against circulatory failure caused by dehydration must be heeded.

Statistical analysis

QQ plots and the Shapiro-Wilk test were used to assess the normality of quantitative data. Data that met normal distribution criteria were described using mean ± standard deviation values. Non-normally distributed data were described using the median [interquartile range (IQR)].

Results

The median age of patients with BOS was 11 (IQR, 8–15) years; 80% were male, and the median body mass index (BMI) was 15.58 (IQR, 11.38–18.68) kg/m^2. Two patients received endotracheal intubation due to respiratory failure before surgery, and no patient received ECLS before surgery. Except for one patient who underwent single LTx due to unilateral lung destruction, the remaining received double LTx. *Table 1* and Table S1 list the baseline and donor data of the ten patients with BOS, respectively.

The surgical duration for pediatric LTx was 5 (IQR, 4–6) hours. Single-lumen tubes were used in four patients because there was no suitable double-lumen bronchial tube. Of the 10 children with BOS, 3 (30%) did not use ECMO, 1 (10%) used peripheral VA-ECMO, and 6 (60%) used central VA-ECMO during the surgery. Propofol, sufentanil, and cisatracurium were used together to maintain anesthesia. The dosages of anesthetic drugs are shown in *Table 2*. All children with BOS received allogeneic red blood cell (RBC) and fresh frozen plasma (FFP) transfusions. The median RBC transfusion volume was 18 (IQR, 14–28) mL/kg, and the median volume of FFP transfusion was 7 (IQR, 0–15) mL/kg. The intraoperative crystalloid volume was 12 (IQR, 8–29) mL/kg; albumin volume was 38 (IQR, 25–48) mL/kg; urine volume was 23 (IQR, 18–50) mL/kg; total input was 84 (IQR, 61–105) mL/kg; and total output was 48 (IQR, 38–79) mL/kg.

All children with BOS underwent TEE during LTx and the parameters before and after the operation were recorded (Table S2). There were no statistically significant differences in the TAPSE before and after the operation

Table 2 Intraoperative characteristics of child patients

Variables	Data (n=10)
Intraoperative CRRT	3 [30]
Intraoperative ECMO	
None	3 [30]
Peripheral VA-ECMO	1 [10]
Central VA-ECMO	6 [60]
Types of intubation	
Tracheal tube	4 [40]
Double lumen tube	6 [60]
Operation time (hours)	5 [4–6]
Anesthesia time (hours)	7 [6–8]
Anesthetics	
Propofol (mg/kg)	42 [32–51]
Sufentanil (μg/kg)	6 [4–8]
Cisatracurium (mg/kg)	1.7 [1.2–2.6]
Blood products	
RBCs (mL/kg)	18 [14–28]
FFP (mL/kg)	7 [0–15]
Albumin (mL/kg)	38 [25–48]
Crystalloids (mL/kg)	12 [8–29]
Urine (mL/kg)	23 [18–50]
Input (mL/kg)	84 [61–105]
Output (mL/kg)	48 [38–79]

Data are presented as n [%] or median [IQR]. CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; IQR, interquartile range; RBC, red blood cell; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

Table 3 Outcomes of child patients who underwent LTx

Variables	Data (n=10)
Postoperative CRRT	
Yes	3 [30]
No	7 [70]
PGD	
<2	9 [90]
≥2	1 [10]
Postoperative AKI	
Yes	4 [40]
No	6 [60]
ICU stay (days)	9 [6–40]
Postoperative ECMO time (hours)	12 [6–12]
Mechanical ventilation (days)	2 [2–24]
Reintubation	
Yes	3 [30]
No	7 [70]
30 days survival	10 [100]

Data are presented as n [%] or median [IQR]. AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; LTx, lung transplantation; PGD, primary graft dysfunction.

(1.21±0.38 *vs.* 1.04±0.36 cm). Although there was no statistically significant difference in left pulmonary vein velocity before and after the operation [82 (IQR, 53–98) *vs.* 90 (IQR, 79–102) cm/s], the postoperative right pulmonary vein velocity was significantly higher than the preoperative levels (79.58±27.41 *vs.* 119.07±46.52 cm/s). All ten children with BOS survived within 30 days after the operation. Only one patient developed PGD grade 3 (PGD3) within 48–72 hours of surgery but 40% of the patients developed acute kidney injury (AKI) within 48 hours after surgery, with ECMO duration of 12 (IQR, 6–12) hours and ICU stay of 9 (IQR, 6–40) days after surgery. *Table 3* shows detailed information on postoperative outcomes.

Discussion

BOS is a common chronic GVHD after HSCT, with a mortality rate of up to 55% (11). LTx is considered for patients with severe BOS who are refractory to conventional treatment and show no signs of recurrence (12). In China, BOS after HSCT is the main indication for cases of pediatric LTx but anesthetic management is a specialized, complex, and challenging task due to factors, including donors, waiting time, and deterioration of recipient function. Reports on best practices for anesthetic management of children with BOS are lacking. In this study, ten children with BOS who underwent double LTx were included, and perioperative data were summarized to elucidate the anesthetic management experience at a single center.

As of June 30, 2018, 2,514 cases of pediatric lung transplant and 733 cases of pediatric heart-lung transplant have been reported to the transplant registry (13). Over the past decade, ISHLT has reported 97–136 pediatric lung transplant cases at 40–50 transplant centers worldwide annually. Most centers perform only 1–4 pediatric lung transplants per year, with only five centers performing more than five surgeries per year. Most pediatric lung transplants are performed in older children, with approximately 70% of the surgeries being performed in children older than 10 years (14). The median survival in cases of pediatric LTx between 1990 and 2015 was 5.4 years (4,14). SAHZU has a 100% 30-day survival rate and a 66.7% 6-month survival rate.

Pediatric lung transplants in cases of BOS involve several critical stages (anesthetic induction, pulmonary artery clamping, pulmonary vein anastomosis, pulmonary artery opening, and ECMO withdrawal). At SAHZU, combined intravenous and inhalational anesthesia is used, and propofol and sevoflurane are preferred. Propofol reduces surgical trauma and inflammatory responses and significantly reduces the incidence of postoperative AKI in patients undergoing LTx (15). Sevoflurane reduces lung ischemia-reperfusion injury by reducing inflammation and oxidative stress (16). Despite the lack of clinical documented literature for their use in cases of pediatric LTx, studies demonstrating the potential risks associated with the use of inhaled anesthetics are insufficient. The goal of anesthesia induction is to maintain hemodynamic stability and to be alert to the occurrence of circulatory failure and malignant arrhythmias under hypovolemia.

After pulmonary artery clamping and graft reperfusion, children with BOS often experience significant hemodynamic fluctuations (17). Hemodynamic monitoring throughout the process is crucial. Although there is no consensus on hemodynamic monitoring during pediatric LTx, in addition to IBP, pulmonary artery, and CVP (18), we monitored PiCCO. However, high-flow ECMO (greater than 1.5 L/min) may affect the hemodynamic parameters obtained by thermodilution technique, especially extravascular lung water (EVLW) (19). Therefore, the potential benefits of using PiCCO during ECMO-bridging LTx in children are unclear.

Intraoperative TEE can quickly identify cardiac dysfunction and ventricular wall motion abnormalities, identify the cause of circulatory instability, and assess volume status. Especially in children, TEE can help identify congenital heart diseases, including patent foramen ovale and endocardial lesions (20). However, sufficient documented literature for using TEE in cases of pediatric LTx is lacking. We referred to the criteria based on previous studies on adults, although this may not be accurate. Therefore, the use of TEE during pediatric LTx warrants greater attention (21).

In recent years, ECMO, as an important method for administering cardiopulmonary support, has been increasingly used in LTx. At SAHZU, all children with BOS who required ECLS were put on ECMO. Although ECMO has been widely used during the perioperative period in adults undergoing LTx to reduce the risk of complications, especially for patients with pulmonary hypertension (22), only a few studies have reported its use in pediatric cases of LTx (23). Parikh *et al.* enrolled 105 children undergoing LTx to determine the ideal form of extracorporeal support in the pediatric population. Compared with cardiopulmonary bypass (CPB) (n=22), the ECMO group (n=13) required a lesser duration of intraoperative support (P=0.018) and showed reduced blood product transfusion (24). However, there was no significant difference in postoperative mortality between the two groups. However, based on the limitations of a small sample size at a single center and the interference of potential confounding factors, compared with CPB, the benefit of ECMO bridging in pediatric cases of LTx requires greater documented literature in support. Simultaneously, we noticed that if it is difficult to maintain adequate oxygenation during one-lung ventilation and there is a potential risk of cardiac dysfunction, the use of ECMO will increase. It should be noted that children with BOS and moderate to severe pulmonary hypertension require great attention as the risk of right heart failure and perioperative death increases (25). Most children with BOS require central VA-ECMO with ascending aorta and right atrium cannulation, which provides CPB-like support. Intraoperative pipeline prefilling is extremely important for ECMO-bridging in cases of pediatric LTx. Because the systemic blood volume of young children is low, allogeneic RBCs are used as the prefilling fluid.

There is a notable absence of guidelines or expert consensus recommendations regarding the indications for the use of ECMO in pediatric LTx. In contrast to adult indications, the criteria for pediatric ECMO at SAHZU include: (I) patients with moderate to severe pulmonary hypertension present prior to transplantation; (II) significant indicators of right heart failure, such as the requirement for positive inotropic support, reduced mixed venous oxygen saturation, and early signs of hepatic and renal dysfunction;

(III) children experiencing respiratory failure (oxygenation index <200 mmHg). Furthermore, VA-ECMO is the preferred mode of support in pediatric LTx. It is important to highlight that pediatric patients exhibit lower tolerance to hemodynamic fluctuations and blood gas alterations, influencing the timing of ECMO initiation. Consequently, SAHZU employs a relatively more proactive ECMO support strategy for pediatric patients. Early initiation of ECMO support is favored in pediatric patients exhibiting early hemodynamic instability or a decreased oxygenation index, in comparison to adult patients. Furthermore, peripheral catheterization presents technical challenges in pediatric patients due to the reduced diameter of their vessels and anatomical variations. Consequently, SAHZU prioritizes central VA-ECMO over peripheral VA-ECMO for pediatric patients, in contrast to the approach taken with adult patients.

The timing of ECMO withdrawal in cases of pediatric LTx is the focus of anesthesiologists. Documented literature for indications for arterial decannulation is lacking but cardiac function, hemodynamic changes, and the dosage of vasoactive drugs warrant close attention. If there is no need to increase the dosage of vasoactive drugs to maintain blood pressure, and no significant cardiac dysfunction is observed after TEE evaluation, gradual reduction of the ECMO flow rate can be tried (by about 1/4–1/3 value each time).

Our approach to ventilation management prioritizes the implementation of a protective ventilation strategy, with the primary objective of minimizing ischemia-reperfusion injury while ensuring sufficient oxygenation and carbon dioxide elimination. Ventilation parameters must be dynamically adjusted in response to real-time monitoring data, which includes lung mechanics, oxygenation indices, and hemodynamics. Given the distinct physiological characteristics of pediatric patients—such as limited respiratory reserve capacity, a reduced compensatory ability for hypoxemia compared to adults, and increased susceptibility to complications associated with mechanical ventilation—it is imperative to exercise stricter control over VT, make more frequent adjustments to ventilation parameters, and develop a more refined and individualized ventilation program. Furthermore, in selecting ventilation modes, PCV modes, such as PCV-VG, are preferred for pediatric patients. In contrast, volume-controlled ventilation is more commonly employed in adult patients. This distinction is based on the high variability in airway compliance and the sensitivity to airway pressure observed in children.

Each additional liter of fluid increases the risk of postoperative PGD3 by approximately 22%. Restricting fluid infusion may reduce the risk of PGD3, early postoperative complications, and mortality (26). However, documented literature for volume management in cases of pediatric LTx is scarce. The functions of various organs in children's bodies have not yet fully matured, and their fluid regulation functions are imperfect, making them more susceptible to disorders due to water and electrolyte imbalance. Therefore, a restrictive fluid replacement strategy remains the first choice but anesthesiologists need to pay attention to the perfusion of important organs, such as the kidney. In terms of fluid types, we did not choose lactated Ringer's solution because it can increase the risk of acidosis. Acetic acid has a wide range of metabolic pathways, is not easy to accumulate, and has the advantage of quickly correcting acidosis and stabilizing the internal environment. Therefore, Plasma-Lyte 148 for fluid resuscitation is our first-line choice. Low-concentration albumin (5%) is the preferred colloid fluid because it can improve the early function of lung allografts, provide better circulatory stability in the early postoperative period, and does not increase the risk of PGD (27). CRRT may be beneficial in preventing pulmonary edema because strictly restrictive fluid replacement and high-dose vasopressors can significantly reduce renal perfusion.

Significant differences in volume management exist between pediatric and adult LTx, primarily due to the unique physiological characteristics of children. Pediatric patients possess a lower blood volume, necessitating precise fluid management. Furthermore, children exhibit a reduced tolerance to volume overload (28) and possess a narrower physiological compensatory range, thereby requiring more stringent infusion strategies and refined monitoring. Volume management in LTx is inherently complex and individualized, with particular challenges arising in pediatric cases due to factors such as open chest procedures, single-lung ventilation, ischemia-reperfusion, and ECMO. Additionally, there remains a lack of consensus regarding rehydration therapy and the use of blood products in LTx (29). At SAHZU, volume therapy in pediatric LTx is co-optimized based on comprehensive hemodynamic monitoring and TEE, among other modalities.

In a manner akin to adults, crystalloids are selected as the primary fluid therapy for children, with Ringer's acetate and saline serving as the predominant intraoperative fluids. Lactated Ringer's solution is avoided due to the potential for lactic acid accumulation following its infusion. However,

dosage calculations in pediatric patients are more intricate, necessitating more precise control of infusion rates. The 'staged' volume management strategy employed at SAHZU parallels that used in adults, albeit with more stringent fluid volume limits for each stage in children.

In pediatric LTx, a more restrictive transfusion strategy is employed compared to adults. Postoperative pediatric patients exhibit a higher susceptibility to pulmonary edema (30), prompting SAHZU to adopt a more conservative transfusion approach than that used for adults. Specifically, intraoperative blood transfusion is generally discouraged in pediatric LTx. At SAHZU, RBC transfusion is indicated when hemoglobin levels fall below 80 g/L. Nonetheless, in instances of concurrent cardiac insufficiency and coagulation disorders, this threshold may be adjusted accordingly. It is advised to maintain the RBC concentration above 25%, with the target value potentially increased based on the patient's hemodynamic status, extent of blood loss, and surgical complications. Additionally, intraoperative monitoring of coagulation factors and platelet function is conducted using thromboelastography (TEG) to guide the administration of FFP, platelets, fibrinogen, and prothrombin complex concentrates.

There are some limitations in this study that warrant further consideration. First, we only summarized our experience of cases of ten children with BOS who underwent LTx at a single center. Nevertheless, the anesthesia management practices outlined in this study provide valuable guidance for the care of pediatric LTx recipients with BOS, offering other institutions the way to draw from our protocols and experience, particularly where existing data are limited. Second, we only followed up on the survival rate within 30 days after surgery, and data on long-term outcomes are lacking. Finally, it is noteworthy that CF and PVD are the most common indications for pediatric LTx in many countries, whereas in China, BOS after HSCT has become the primary indication. This regional difference may limit the generalization of our findings to other populations. Future studies should consider these differences when comparing pediatric LTx outcomes in different regions.

Conclusions

In conclusion, we summarize the experience of anesthesia management during LTx in children with BOS. Preoperative evaluation, volume management, hemodynamic monitoring, and the use of TEE and ECMO are the key points for anesthesiologists. LTx in children with BOS is extremely risky, and we emphasize the necessity of multidisciplinary collaboration during the perioperative period.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Human Body Research Ethics Committee of The Second Affiliated Hospital of Zhejiang University School of Medicine (No. 2022-0352). The requirement for written informed consent was waived because of the retrospective observational design of the study.

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