Preoperative Hypercapnia as a Predictor of Hypotension during Anesthetic Induction in Lung Transplant Recipients

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Abstract

Objective. To determine the incidence and predisposing factors of hypotension during anesthetic induction in lung transplant recipients.

Design. Retrospective study

Setting. University hospital

Participants. Patients who underwent lung transplantation between 2008 and 2013 (n = 68).

Interventions. None

Measurements and Main Results. We analyzed the mean arterial blood pressure (MAP) from administration of anesthetic drugs to 10 min after endotracheal intubation (i.e., the anesthetic induction) among participants who underwent lung transplantation. Patients were considered to have clinically significant hypotension (CSH) when the following criteria were fulfilled: a MAP decrease of >40% from baseline and MAP of <60 mmHg. Overall, 41.2% of patients experienced CSH during the induction of anesthesia. The preoperative partial pressure of carbon dioxide ($PaCO_2$) was significantly higher in patients who experienced CSH during anesthetic induction than in those who did not (P = 0.005). Preoperative $PaCO_2$ predicted the development of CSH during anesthetic induction (area under the curve = 0.702; P = 0.002) with an optimal cut-off point of 55 mmHg determined by maximizing the Youden index. The incidences of CSH during anesthetic induction for patients with ($PaCO_2 \geq 55$) and without ($PaCO_2 < 55$) preoperative hypercapnia were 75.0% [95% confidence interval (CI) (53.8–89.2)] and 30.8% (95% CI 26.4–37.3), respectively. After adjustment for known predicting factors, the odds ratio for the relationship between preoperative hypercapnia and CSH during anesthetic

induction was 12.54 (95% CI 3.10–66.66).

Conclusions. Hypotension during anesthetic induction is common in lung transplant recipients, and is independently predicted by preoperative hypercapnia.

Key words: lung transplantation, anesthetic induction, hypotension, hypercapnia

Introduction

Inducing anesthesia and commencing positive-pressure ventilation are the first critical events in the anesthetic management of lung transplantation, which is the definitive treatment for end-stage lung disease among patients that are nonresponsive to medical therapy.[1] Lung transplant recipients are at a risk of severe hypotension and even cardiac arrest during the induction period, and most authorities recommend close hemodynamic monitoring.[2, 3, 4] It would be useful to predict those patients at a risk of severe hypotension during this period because anesthesiologists may be distracted immediately after induction by several tasks such as airway management, ventilator adjustments, and the placement of pulmonary artery catheters. However, the hemodynamic responses or the predisposing factors associated with hypotension during the anesthetic induction in lung transplant recipients are not completely understood.

We analyzed the hemodynamic changes during the anesthetic induction in a cohort of lung transplant recipients, to determine the incidence of clinically significant hypotension (CSH) and to explore the characteristics of patients who experienced hemodynamic instability during that period.

Methods

After obtaining the approval of the Institutional Review Board (the approval number: E2094), we retrospectively reviewed the electronic medical records of consecutive 75 patients who underwent lung transplantation at Kyoto University Hospital between 2008 and 2013. We excluded those patients who were intubated or who received a preoperative tracheostomy. We collected specific data from the medical records of participants, including patient characteristics (age, gender, height, body mass index, preexisting lung disorder,

and Hugh-Jones classification) and preoperative examination findings (arterial blood gas analysis, transthoracic echocardiography, and pulmonary function test). Preoperative arterial blood gas analysis was conducted within a one week period prior to the surgery.

For the anesthetic induction, patients were managed using the following technique, without receiving premedication. Upon entering the operation room, we obtained peripheral intravenous access, and commenced pulse oximetry, electrocardiography, and noninvasive blood pressure monitoring. In addition, an arterial catheter was placed before anesthetic induction, except for five children (age 8–12 years) in whom the arterial catheter was placed after anesthetic induction and endotracheal intubation. Preoxygenation was performed for at least 3 min prior to induction in all cases. We employed rapid induction with propofol or midazolam plus opioids in all but one patient who had difficulty opening their mouth; therefore, in this case we used semiconscious fiberoptic intubation. Rocuronium was used to facilitate endotracheal intubation, following bag and mask ventilation. Sevoflurane was used to maintain anesthesia in all cases. Hypotension during anesthetic induction was treated with a bolus administration of ephedrine or phenylephrine. In cases with refractory hypotension, a continuous noradrenaline infusion was initiated. The anesthetic induction period was defined as the period from administration of anesthetic drugs (propofol or midazolam) to 10 min after endotracheal intubation. We collected data on the mean arterial blood pressure (MAP) and heart rate during this period. The MAP and heart rate were automatically recorded every minute by an anesthesia information management system (Nihon Kohden, Tokyo, Japan). The baseline MAP and heart rate were defined as the median value of all recordings before anesthetic induction (the preinduction period). The medians were chosen as the best

method for filtering out data artifacts.5 Patients were considered to have CSH when the following criteria were fulfilled: a MAP decrease of >40% from baseline and MAP of <60 mmHg.

Statistical analysis

Data were analyzed using JMP version 8.0 (SAS Institute Japan Ltd., Tokyo, Japan). Continuous data are presented as median (range), whereas categorical variables are expressed as a number (percentage). Differences between groups were compared using the Mann–Whitney U test for continuous variables. For categorical variables, Pearson chi-square or Fisher exact tests were used as appropriate. All the statistical tests were two tailed and the statistical significance was set at $P < 0.05$.

To evaluate the ability of the $PaCO_2$ to predict CSH during the anesthetic induction, we performed receiver operating characteristic curve (ROC) analysis. The optimal cut-off point was determined by maximizing the Youden index (sensitivity + specificity − 1). Multivariate logistic regression analysis was performed to assess the independent role of preoperative hypercapnia in the development of CSH. All covariates considered were entered into multivariate analysis for which a backward elimination was performed to seek independent factors associated with CSH. All variables maintaining a P value of <0.1 were included in the final model.

Results

A total of 75 patients underwent lung transplantation during the study period. Of these, we analyzed 68 eligible patients after excluding six patients who received a tracheostomy and one who was intubated before entering the operating room. The clinical characteristics of the study population are described in Table 1. The age of the patients ranged from 8 to 64 years, and we included nine children <18 years. Preoperative $PaCO_2$

ranged from 28.7 to 104.0 mmHg and the median value was 47.7 mmHg. Two patients received preoperative noninvasive positive pressure ventilation.

Hemodynamic changes during anesthetic induction are summarized in Table 2. The maximum decrease in MAP from baseline ranged from 0% to 79.1%, with a median value of 39.1%. During anesthetic induction, 28 patients (41.2%) developed CSH, although no patient developed severe bradycardia (HR < 50). Forty-four patients (64.7%) received vasoactive drugs and 14 (20.6%) received a continuous noradrenaline infusion during the induction period. Accumulated dose of ephedrine during the induction period ranged from 0 to 12 mg, while phenylephrine ranged from 0 to 0.4 mg. The infusion rate of noradrenaline during the induction period ranged from 0 to 0.2 μg/kg/min. The characteristics of the study population that developed CSH during the induction period are summarized in Table 3. Among the variables, preoperative $PaCO_2$ (P = 0.005) and preoperative pH (P = 0.005) were significantly associated with the development of CSH during anesthetic induction. Although the difference of preoperative pH between patients with and without CSH was statistically significant, the median preoperative pH for both groups were within the normal range (7.41 versus 7.37) and the clinical significance of the difference was very little. So, thereafter we only analyzed $PaCO_2$ as a potential predisposing factor for CSH during anesthetic induction.

The ROC analysis revealed that preoperative $PaCO_2$ was significantly predictive of CSH during anesthetic induction [area under the curve = 0.702, 95% confidence interval (CI) 0.557–0.815, P = 0.002; Figure]. In selecting optimal cut-off values for the effect of preoperative $PaCO_2$ on the development of CSH during anesthetic induction, the range between the 10th and the 90th percentile (36.8–66.7 mmHg) was selected for

the distribution of preoperative $PaCO_2$ and we considered possible cut-off points at 5-mmHg intervals from 40 mmHg to 65 mmHg (giving six candidate cut-off points). The most discriminant cut-off value of $PaCO_2$ determined by maximizing the Youden index was 55 mmHg, which predicted CSH during anesthetic induction with a sensitivity of 43% (95% CI 31–51) and a specificity of 90% (95% CI 82–96) (Table 4). The incidence of CSH during anesthetic induction was 75.0% (95% CI 53.8–89.2) for the patients with preoperative hypercapnia (preoperative $PaCO_2 \geq 55$), and 30.8% (95% CI 26.4–37.3) for those without preoperative hypercapnia (preoperative $PaCO_2 < 55$).

Finally, we conducted multivariate logistic regression analysis to assess the independent role of preoperative hypercapnia in the development of CSH during the induction period. We considered the following known predisposing factors for hypotension during anesthetic induction as potential confounding factors: age, use of propofol for anesthetic induction, and the presence of pulmonary hypertension (systolic pulmonary artery pressure estimated to be ≥40 mmHg on preoperative transthoracic echocardiography).[5, 6] Propofol dosing was coded into three categories: 1 = no propofol use for anesthetic induction; 2 = <1.4mg/kg; 3 = ≥1.4mg/kg. In addition, preoperative pH of <7.35 was also considered as a potential predisposing factor to assess the effect of uncompensated respiratory acidosis compared to chronically compensated respiratory acidosis. After stepwise backward elimination, the variables that remained in the final model as independent predisposing factors of CSH were age, preoperative hypercapnia, and pulmonary hypertension (Table 5). Among them, preoperative hypercapnia was the most significant predisposing factor (P = 0.001).

Discussion

The primary aim of this study was to determine the incidence of CSH during anesthetic induction in lung transplant recipients. We found that the median decrease in MAP during anesthetic induction was 39.1%, and 41.2% of patients experienced CSH. Although it is difficult to compare the incidence of hypotension with other studies because of the use of different definitions of hypotension, the decrease in MAP was substantially higher than that reported in previous studies, in which the degree of MAP decrease during anesthetic induction with propofol was reported to be 24.6%–26.0%.[7, 8, 9] We should consider lung transplant recipients to be at high risk of hypotension during anesthetic induction. Vigilance is essential during the induction period, and it may be appropriate to consider prophylactic femoral cannulation in those at highest risk.

Dehydration and pulmonary hypertension may have contributed to the high incidence of hypotension during anesthetic induction. Patients with end-stage lung disease are generally at least moderately hypovolemic due to diuretic use or increased insensible losses from work of breathing.[10] Most lung transplant recipients have pulmonary hypertension and right ventricular dysfunction to some extent,[11] and they often have pulmonary vascular medial wall hypertrophy, which increases the potential for sudden increases in pulmonary vascular resistance and right heart failure.[12, 13] These factors may exaggerate the myocardial depressant or vasodilatory effects of anesthetic agents and lead to significant hemodynamic instability.

We identified preoperative hypercapnia as an independent predisposing factor for CSH during anesthetic induction. To the best of our knowledge, no previous study has reported such an association. When the cut-off for preoperative $PaCO_2$ was set at 55 mmHg, preoperative hypercapnia predicted CSH during the induction period with high specificity (90%, 95% CI 82–96). In addition, the adjusted odds ratio for the relationship

between preoperative hypercapnia and CSH was high, at 12.54 (95% CI 3.10–66.66). Patients with preoperative hypercapnia should be considered at high risk of hypotension during the anesthetic induction.

The reason for the association between preoperative hypercapnia and hypotension during the anesthetic induction is unclear; however, there are possible explanations. More severe dehydration due to increased work of breathing may exist in patients with preoperative hypercapnia and may make them more susceptible to the myocardial depressant or vasodilatory effects of anesthetic agents. Higher airway pressures may be needed for positive pressure ventilation among patients with severe lung disease who present with preoperative hypercapnia, which restricts systemic venous return and may cause hypotension.

Attention should be paid to the low sensitivity of preoperative hypercapnia in this study. Although preoperative hypercapnia ($PaCO_2 \geq 55$ mmHg) had a high specificity (90%), it also had a low sensitivity (43%) for CSH during anesthetic induction, which implies that 57% of CSH could be missed. Not only preoperative hypercapnia but also other factors may be contributing to CSH.

Rapid propofol induction for lung transplant recipients may also be criticized because it has been implicated in the development of hypotension.[5, 14] A narcotic-based "cardiac anesthetic" with slow titration of the induction agent may provide improved hemodynamic stability.[4, 10] However, slow titration of the induction agent may increase the risk of hypoventilation and oxygen desaturation during induction because it takes more time to induce anesthesia and secure the airway. Consequently, rapid induction with propofol or midazolam tends to be preferred for lung transplant recipients. The method of anesthetic induction should be selected based on a careful risk–benefit analysis.

The period before the induction of general anesthesia is typically a time of heightened anxiety, which may temporarily increase the baseline blood pressure. If we use only the degree of MAP decrease to define CSH, increased baseline pressure may cause overestimation of the incidence of CSH. On the other hand, defining CSH solely on the basis of absolute value of MAP (MAP of <60 mmHg, for example) may not be appropriate in some population, for example, in pediatric patients. We attempted to control the influence of the baseline blood pressure using the following criteria to define CSH: MAP decrease of >40% and MAP of <60 mmHg. This study suffers certain limitations based primarily on its retrospective design. The fluid therapy, positional changes, or other potential confounders that may have influenced these results are unknown. Furthermore, there was no predefined protocol for rescue administration of vasopressors.

In conclusion, we found that there is a high incidence (41.2%) of CSH during anesthetic induction in lung transplant recipients and that preoperative hypercapnia appears to be an independent predisposing factor.

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Table 1. Preoperative characteristics of the study population (n = 68)

	Median (range) or number (percentage)
Age (years)	43 (8–64)
Female gender	30 (44.1%)
Height (cm)	161 (116–179)
Body mass index (kg/m^2)	17.9 (10.8–28.5)
Preexisting lung disorder	
Pulmonary fibrosis	23
Bronchiolitis obliterans	18
Emphysema	7
Pulmonary hypertension	5
Others	15
Hugh–Jones classification (III/IV/V)	5/40/23
Preoperative NIPPV	2 (2.9%)
Pulmonary function test	
VC (L)	1.56 (0.17–3.81)
%VC (%)	47.4 (10.2–116.2)
FEV_1 (L)	0.82 (0.15–2.57)
%FEV_1 (%)	29.8 (5.1–84.8)
Transthoracic echocardiography	
Left ventricular ejection fraction	69.3 (44.0–91.0)
Pulmonary hypertension	26 (38.2%)
Resting arterial blood gas analysis	
pH	7.39 (7.27–7.49)
$PaCO_2$	47.7 (28.7–104.0)

NOTE. Pulmonary function tests were not conducted in seven patients because of their medical condition.

Patients were considered to have pulmonary hypertension when the systolic pulmonary artery pressure (estimated in transthoracic echocardiography) was ≥40 mmHg.

Abbreviations: NPPV, noninvasive positive pressure ventilation; VC, vital capacity; FEV_1, forced expiratory volume in 1 s; $PaCO_2$, partial pressure of carbon dioxide

Table 2. Details of anesthetic induction

	Median (range) or number (percentage)
Induction agent	
Midazolam	49 (72.1%)
Propofol	21 (30.9%)
Rocuronium	68 (100%)
Fenanyl	17 (25.0%)
Remifentanil	59 (86.8%)
HR before induction	101 (65–153)
Minimum HR	89 (56–135)
MAP before induction	96 (55–139)
Minimum MAP	58 (19–98)
The degree of decrease in MAP	39.1 (0.0–79.1)
Vasoactive drugs	
Ephedrine	7 (10.3%)
Phenylephrine	31 (45.6%)
Noradrenalin	14 (20.6%)
None	24 (35.3%)
Arterial blood gas analysis after induction	
PaO_2/FiO_2 ratio	468.5 (75.0–639.0)
pH	7.35 (6.96–7.60)
$PaCO_2$	52.7 (22.2–192.1)

NOTE. Degree of decrease in MAP was calculated as follows: (MAP before induction - lowest MAP during induction)/MAP before induction.

Abbreviations: HR, heart rate; MAP, mean arterial pressure; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen

Table 3. Univariate Analysis of Potential Predictors of Hypotension during Anesthetic Induction

Variable	No Hypotension (n = 40)	Hypotension (n = 28)	*P* value
Age	38 (8–62)	46 (10–64)	0.159
Female gender	15 (37.5%)	15 (53.6%)	0.189
Height (cm)	164 (116–179)	159 (125–172)	0.145
Body mass index (kg/m^2)	17.8 (11.1–28.5)	18.4 (10.8–25.8)	0.856
Original disease			0.714
Pulmonary fibrosis	16 (40.0%)	8 (28.6%)	
Bronchiolitis obliterans	9 (22.5%)	9 (32.1%)	
Emphysema	3 (7.5%)	4 (14.3%)	
Pulmonary hypertension	4 (10.0%)	2 (7.1%)	
Others	8 (20.0%)	5 (17.9%)	
Hugh-Jones classification (III/IV/V)	2/27/11	3/13/12	0.21
Preoperative pulmonary function test			
%VC	48.3 (16.9–99.5)	47.0 (10.2–116.2)	0.726
$\%FEV_1$	32.7 (11.9–84.8)	26.3 (5.1–71.2)	0.331
Transthoracic echocardiography			
Left ventricular ejection fraction	68.7 (64.8–73.9)	70.7 (64.2–76.6)	0.454
Pulmonary hypertension	12 (30.0%)	14 (50.0%)	0.095
Resting arterial blood gas analysis			
pH	7.41 (7.35–7.49)	7.37 (7.27–7.46)	0.005
$PaCO_2$	45.4 (28.7–77.3)	53.0 (35.2–104.0)	0.005
Baseline mean arterial pressure	96 (55–127)	97 (73–139)	0.695
Baseline heart rate	97 (65–153)	105 (72–136)	0.203
Use of propofol for anesthetic induction	15 (37.5%)	7 (25.0%)	0.278
Use of remifentanil for anesthetic induction	35 (87.5%)	24 (85.7%)	0.831

NOTE. Pulmonary function tests were not conducted in two patients who experienced and in five patients who did not experience hypotension during anesthetic induction. Left ventricular ejection fraction was not evaluated in patients who did not experience hypotension during anesthetic induction. The patient was

considered to have pulmonary hypertension when the systolic pulmonary artery pressure (estimated in transthoracic echocardiography) was ≥40 mmHg.

Abbreviations: VC, vital capacity; FEV_1, forced expiratory volume in 1 s; $PaCO_2$, partial pressure of carbon dioxide

Table 4. Cut-off Analysis for Preoperative $PaCO_2$ and Clinically Significant Hypotension

Preoperative $PaCO_2$	Uncorrected odds ratio (95% CI)	Sensitivity	Specificity	Youden index	Uncorrected P value
40	3.57 (0.90–14.13)	0.893	0.3	0.193	0.059
45	3.00 (1.04–8.63)	0.75	0.5	0.25	0.038
50	3.46 (1.23–9.71)	0.536	0.75	0.286	0.016
55	6.75 (1.88–24.17)	0.429	0.9	0.329	0.002
60	9.00 (1.77–45.85)	0.321	0.95	0.271	0.003
65	4.13 (0.74–23.06)	0.179	0.95	0.129	0.086

Abbreviations: $PaCO_2$, partial pressure of carbon dioxide; CI, confidence interval

Table 5. Multivariate Analysis of Independent Predisposing Factors for Clinically Significant Hypotension during Anesthetic Induction

Variables	Coefficient	SE	Adjusted odds ratio (95% CI)	P value
Intercept	−3.14	1.00		
Age	0.04	0.02	1.04 (1.00–1.08)	0.037
Preoperative hypercapnia	2.53	0.77	12.54 (3.10–66.66)	0.001
Pulmonary hypertension	1.38	0.62	3.97 (1.24–14.17)	0.025

Note. Patients were considered to have pulmonary hypertension when the systolic pulmonary artery pressure (estimated in transthoracic echocardiography) was ≥40 mmHg.

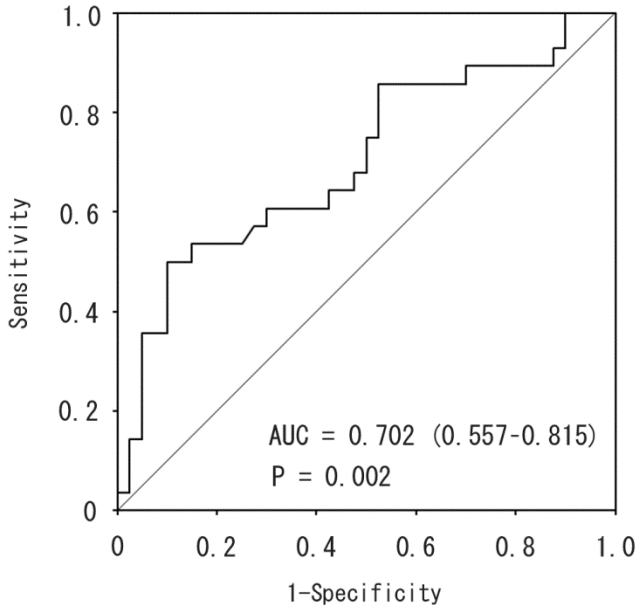
Abbreviations: SE, standard error; CI, confidence interval

Figure caption

Figure. Receiver operating characteristic (ROC) curve for the prediction of clinically

significant hypotension using preoperative partial pressure of carbon dioxide. AUC, area

under the ROC curve, with 95% confidence interval given in parentheses.


1.0
0.8
0.6
0.4
0.2
0
Sensitivity
0
0.2
0.4
0.6
0.8
1.0
1-Specificity
AUC = 0.702 (0.557-0.815)
P = 0.002

The clinical course of anesthetic induction in lung transplant recipients with pulmonary complications after hematopoietic stem cell transplantation

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Key words: lung transplantation, hematopoietic stem cell transplantation (HSCT), anesthesia, dynamic compliance, oxygen desaturation

Abstract

Purpose: We examined the clinical course of anesthetic induction in lung transplant recipients with pulmonary complications after hematopoietic stem cell transplantation (post-HSCT), focusing on ventilatory management. We aimed to determine the incidence of oxygen desaturation during anesthetic induction and severe respiratory acidosis after anesthetic induction in post-HSCT lung transplant recipients, and to explore factors associated with their development.

Methods: Nineteen consecutive patients who underwent lung transplantation post-HSCT at Kyoto University Hospital (Japan) were retrospectively studied. Data regarding patient characteristics, preoperative examination, and clinical course during anesthetic induction were analyzed.

Results: The incidence of oxygen desaturation (SpO_2 < 90%) during anesthetic induction and severe respiratory acidosis (pH < 7.2) after anesthetic induction were 21.1% and 26.3%, respectively. Reduced dynamic compliance (Cdyn) during mechanical ventilation was significantly associated with oxygen desaturation during anesthetic induction (P = 0.01), as well as severe respiratory acidosis after (P = 0.01). The preoperative partial pressure of carbon dioxide in arterial blood ($PaCO_2$; r = −0.743, P = 0.002) and body mass index (BMI; r = 0.61, P = 0.021) significantly correlated with Cdyn, and multivariate analysis revealed that both $PaCO_2$ and BMI were independently associated with Cdyn.

Conclusion: Oxygen desaturation during anesthetic induction and severe respiratory acidosis after anesthetic induction frequently occur in post-HSCT lung transplant recipients. Low Cdyn may, at least partially, explain

oxygen desaturation during anesthetic induction and severe respiratory acidosis after anesthetic induction. Moreover, preoperative hypercapnia and low BMI were predictive of low Cdyn.

Introduction

Late-onset pulmonary complications, including bronchiolitis obliterans (BO), are frequent critical issues after hematopoietic stem cell transplantation (HSCT) [1]. Bronchiolitis obliterans, part of the chronic graft versus host disease (cGVHD) spectrum of manifestations [2], affects 5.5% of allogeneic HSCT recipients and 14% of those who develop cGVHD [3]. So far, the prognosis of patients with moderate to severe BO is dismal [4].

Several studies have recently reported acceptable outcomes following lung transplantation for pulmonary complications post-HSCT. Thus, lung transplantation post-HSCT is considered to be a viable therapeutic option for patients cured of their hematologic disease and whose only significant morbidity is end-stage lung disease [5–9]. However, to the best of our knowledge, there are no reports regarding anesthetic management of lung transplant recipients post-HSCT.

In this study, we examined the clinical course of anesthetic induction in post-HSCT lung transplant recipients, focusing on ventilatory management. The purposes of the current study were as follows: (1) to examine the incidence of oxygen desaturation during anesthetic induction and severe respiratory acidosis after anesthetic induction in post-HSCT lung transplant recipients, and (2) to explore the factors associated with development of oxygen desaturation or severe respiratory acidosis. To the best of our knowledge, this is the first report to investigate anesthetic management of lung transplant recipients post-HSCT.

Methods

This retrospective cohort study was approved by the ethics committee of Kyoto University Hospital, Japan (approval number: E2094). All patients who underwent lung transplantation post-HSCT at Kyoto University

Hospital from January 1, 2008, to December 31, 2012, were eligible for this study. Medical records of eligible patients were reviewed with regard to patient characteristics, preoperative examination, and clinical course during anesthetic induction.

In all cases, preoperative arterial blood gas analysis was conducted during the period from one week before the surgery to the day before the surgery. Anesthetic induction of patients was managed using the following technique without premedication. Preoxygenation was performed at least 3 min prior to induction in all cases. Rapid induction with propofol or midazolam plus opioids was completed in all but one patient who had difficulty opening their mouth; in this case, we used semiconscious fiber-optic intubation. Rocuronium was used to facilitate endotracheal intubation following bag and mask ventilation. For mechanical ventilation after endotracheal intubation, Fabius Tiro (Dräger, Lübeck, Germany) or Apollo Anesthesia Workstation (Dräger) was used. The adjustment of ventilator settings was done by the attending anesthesiologist. The anesthetic induction period was defined as the period from administration of anesthetic drugs (propofol or midazolam) to 10 min after endotracheal intubation, and arterial oxygen saturation of hemoglobin (SpO_2) data during this period was collected. Oxygen desaturation was defined as SpO_2 of <90%. The peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), respiratory rate (RR), and tidal volume (TV) at three time points (10, 20, and 30 min after intubation) were obtained directly from the ventilator. Dynamic compliance (Cdyn) was calculated with the following equation: $Cdyn = TV/(PIP - PEEP)$. We then calculated the mean value of each variable (PIP, PEEP, RR, TV, and Cdyn) at each time point.

Because this study included 7 children under 20 years of age, TV and Cdyn were adjusted for ideal body

weight (IBW). Ideal body weight was determined with the body mass index (BMI) method [10, 11]. For children under 20 years of age, the 50th percentile BMI for age, height, and gender on the Centers for Disease Control BMI-for-age percentiles chart [12] was used.

Arterial blood gas analysis was conducted after anesthetic induction and establishment of mechanical ventilation. The median time from endotracheal intubation to arterial blood gas analysis was 23 min (range: 10–60 min). Severe acidosis was defined as pH < 7.2.

Statistical analysis

Data were analyzed using the statistical program R (http://cran.r-project.org) and are presented as median (range) and percentage unless stated otherwise. Differences between groups were compared using the Mann–Whitney U test for continuous variables. For categorical variables, the Pearson chi-square or Fisher exact test was used where appropriate. Linear regression analysis was used to assess correlations between continuous variables. Multivariate forward stepwise analysis was used to assess independent determinants of Cdyn. All statistical tests were two-tailed, and statistical significance was set at $P < 0.05$.

Results

Patient characteristics and preoperative examination

A total of 19 post-HSCT patients underwent lung transplantation during the study period; 14 (73.7%) patients underwent living-donor lobar lung transplantation and five (26.3%) underwent cadaveric lung transplantation (Table 1). Fifteen (78.9%) patients developed respiratory symptoms within 3 years of HSCT, and the median interval from respiratory symptom onset to lung transplantation was 38 months (range: 7–137 months). All

except one patient were preoperatively diagnosed with BO. At the time of lung transplantation, eight patients (42.1%) could ambulate; two (10.5%) received noninvasive positive pressure ventilation (NPPV), and two (10.5%) received preoperative tracheostomy.

A pulmonary function test (PFT) was conducted in 15 (78.9%) patients from onset of respiratory symptoms to lung transplantation. In the remaining four patients, PFT could not be performed because of pneumothorax (two patients), tracheostomy (one patient), or severe respiratory symptoms (one patient). The median interval from PFT to lung transplantation was 12 months (range: 0.5–52 month), and the interval was longer than 1 year in five patients. For these five patients, follow-up PFT could not be performed because of pneumothorax (three patients) or severe respiratory symptoms (two patients). In PFT, all patients exhibited reduction in forced expiratory volume in 1 s (FEV_1; range: 4–43% predicted) and forced vital capacity (FVC; range: 2–65% predicted). Ten patients exhibited typical obstructive lung defect ($FEV_1/FVC < 0.7$). In five patients, FEV_1 and FVC decreased concomitantly, whereas the FEV_1/FVC ratio remained >0.7.

Preoperative hypercapnia ($PaCO_2 > 45$ mmHg) was seen in 16 (84.2%) patients. Although nine (47.4%) patients exhibited severe preoperative hypercapnia ($PaCO_2 > 60$ mmHg), no patient exhibited severe acidosis (pH < 7.2) preoperatively.

Clinical course during anesthetic induction

Table 2 presents the main characteristics of anesthesia induction. Four (21.1%) patients experienced oxygen desaturation ($SpO_2 < 90\%$) during anesthetic induction. Oxygen desaturation occurred during the period from administration of anesthetic drugs to endotracheal intubation in all cases, and the duration of oxygen

desaturation ranged from 1 to 7 min. High PIP (median: 26.7 cmH_2O) and RR (median: 20/min) were required for mechanical ventilation after anesthetic induction. The median Cdyn per IBW was 0.21 $mL/cmH_2O/kg$, and three patients exhibited Cdyn < 0.1 $mL/cmH_2O/kg$. Five (26.3%) patients exhibited severe respiratory acidosis (pH < 7.2) after anesthetic induction. Although pH recovered to an acceptable range (pH ≥ 7.2) after adjusting ventilator settings in three of these cases, two required emergency cardiopulmonary bypass because of hemodynamic instability related to acidemia, which resulted from hypercapnia after anesthetic induction.

We further explored factors associated with development of oxygen desaturation during anesthetic induction and severe respiratory acidosis after anesthetic induction. Characteristics of patients with/without oxygen desaturation during anesthetic induction are described in Table 3. All four patients with oxygen desaturation could not ambulate preoperatively; one received NPPV and another received tracheostomy. Dynamic compliance was significantly lower in patients with oxygen desaturation (P = 0.01), and all patients with oxygen desaturation exhibited severe respiratory acidosis after anesthetic induction. Although the ratio of partial pressure of oxygen in arterial blood to the fraction of inspired oxygen (PaO_2/F_IO_2) after anesthetic induction tended to be lower in those with oxygen desaturation, the difference did not reach statistical significance. Characteristics of patients with/without severe respiratory acidosis after anesthetic induction are described in Table 4. Four out of five patients with severe respiratory acidosis also experienced oxygen desaturation during anesthetic induction. Unability to ambulate, low FVC, high preoperative $PaCO_2$, and low Cdyn were significantly associated with development of severe respiratory acidosis after anesthetic induction. Among these factors, low Cdyn was the most significantly associated with development of severe respiratory

acidosis (P = 0.01).

Predisposing factors of low Cdyn

Because low Cdyn was significantly associated with both oxygen desaturation during anesthetic induction and severe respiratory acidosis after anesthetic induction, we explored preoperative factors associated with low Cdyn. Bivariate analyses, performed to test the relationship between Cdyn and preoperative parameters (age, gender, BMI, preoperative $PaCO_2$, FEV_1, and FVC), showed preoperative $PaCO_2$ to be strongly associated with Cdyn ($r = -0.743$, $P = 0.002$). BMI was also significantly associated with Cdyn ($r = 0.61$, $P = 0.021$). However, neither FEV_1 nor FVC were significantly associated with Cdyn (Figure 1).

In order to assess the independent determinants of Cdyn, a forward stepwise regression analysis was conducted, which included age, gender, BMI, preoperative $PaCO_2$, ventilation mode (volume or pressure control ventilation), and type of tracheal tube (single or double lumen tube). Analysis revealed that preoperative $PaCO_2$ and BMI were significantly associated with Cdyn (Table 4).

Discussion

Analysis of our cohort revealed the following: (1) oxygen desaturation during anesthetic induction and severe respiratory acidosis after anesthetic induction frequently occurred in lung transplant recipients post-HSCT, (2) low Cdyn during mechanical ventilation was significantly associated with oxygen desaturation during anesthetic induction and severe respiratory acidosis after anesthetic induction, and (3) preoperative $PaCO_2$ and BMI were significantly associated with Cdyn.

Although anesthesia was induced after preoxygenation, four (21.1%) patients experienced oxygen

desaturation during anesthetic induction. In all four cases, oxygen desaturation occurred during the period from anesthetic drug administration to endotracheal intubation. Moreover, low Cdyn was significantly associated with development of oxygen desaturation, and all of four patients with oxygen desaturation exhibited severe respiratory acidosis after anesthetic induction. Therefore, we concluded that difficulty in bag and mask ventilation after cessation of spontaneous breathing due to low lung-thorax compliance contributed, at least partially, to the development of oxygen desaturation during anesthetic induction. Lung transplant recipients post-HSCT should be considered as high risk for difficult bag and mask ventilation.

In this study, five (26.3%) patients exhibited severe respiratory acidosis after anesthetic induction. As expected, low Cdyn was significantly associated with severe respiratory acidosis after anesthetic induction. Ventilator strategies that use low tidal volume and allow permissive hypercapnia have been shown to be beneficial in patients with adult respiratory distress syndrome, a disease characterized by low compliance [13]. Similarly, $PaCO_2$ levels as high as 60 mmHg are commonly accepted in ventilatory management during lung transplantation, and levels as high as 120 mmHg have been reported without adverse sequelae [14–16]. However, acute hypercapnia and acidosis can exacerbate pulmonary hypertension and cause hemodynamic instability [17,18]. Because most patients with severe lung disease have some degree of pulmonary hypertension and possibly a hyper-responsive pulmonary vascular wall [19], they may be susceptible to hypercapnia or acidosis. Therefore, close monitoring of $PaCO_2$ and adjustment of ventilatory settings are essential for safe anesthetic management of lung transplant recipients with reduced lung-thorax compliance. Continuous $PaCO_2$ monitoring [20] may be useful for real-time monitoring of $PaCO_2$ during anesthesia for

lung transplant recipients.

The median Cdyn per IBW among our study population was 0.21 mL/cmH_2O/kg. Previous studies have reported Cdyn in mechanically ventilated adults without lung diseases to be 32.0–59.7 mL/cmH_2O [21,22]. In addition, in a study that examined the ventilatory mechanics of pediatric patients after cardiac surgery, Cdyn adjusted for weight was reported as 0.67 mL/cmH_2O/kg [23]. In our study population, Cdyn was substantially lower than those reported in previous studies. Most patients in our study were diagnosed with BO, which is characterized by an obstructive PFT pattern and evidence of air trapping on chest computed tomography [24]. However, histological features post-HSCT are heterogeneous [25], and post-HSCT patients present several PFT phenotypes, including restrictive or combined ventilatory impairment [26]. In our study, all patients who underwent PFT presented a moderate to severe reduction in FVC. Reduced elasticity of the lungs combined with air trapping caused by positive pressure ventilation may have resulted in extremely low Cdyn values.

Preoperative $PaCO_2$ strongly correlated with Cdyn, whereas preoperative FEV_1 and FVC did not. PFT may not be suitable for assessment of respiratory status at the time of lung transplantation because it is difficult to perform just before surgery, especially in cadaveric lung transplantation, which is always conducted in emergent settings. Moreover, PFT cannot be performed in patients with pneumothorax, tracheostomy, or extremely bad respiratory status. In our study, PFT was not conducted in four patients, and the intervals from PFT to lung transplantation were longer than 1 year in five patients. In contrast, arterial blood gas analysis is very useful for assessing the respiratory status of very ill patients because it can be performed bedside and in a very short time. Patients with preoperative hypercapnia should be considered at risk of low lung-thorax

compliance, and therefore, oxygen desaturation during anesthetic induction due to difficulty in bag and mask ventilation, as well as severe respiratory acidosis after anesthetic induction. It may be appropriate to consider prophylactic femoral cannulation in patients at highest risk.

BMI was positively correlated with Cdyn in both univariate and multivariate analyses. These results appear to be inconsistent with the well-known fact that respiratory compliance is reduced in obese patients [27]. However, this study did not include obese patients, but instead included twelve (63.2%) patients with a BMI < 17 kg/m^2. Thus, a low BMI may reflect the severity of respiratory dysfunction.

The major limitation of this study was its retrospective design and small sample size. Because our study included a small number of patients, there is a large chance of type II error, i.e., factors that affect the development of oxygen desaturation or severe respiratory acidosis may have been missed. Additional limitations included the fact that data collected in this study was derived from one institution and that ventilator settings after anesthetic induction were not uniform. Despite these limitations, our data provide new information regarding the anesthetic management of post-HSCT lung transplant recipients.

In conclusion, oxygen desaturation during anesthetic induction and severe respiratory acidosis after anesthetic induction frequently occur in post-HSCT lung transplant recipients. Low Cdyn may, at least partially, explain oxygen desaturation during anesthetic induction and severe respiratory acidosis after anesthetic induction. Furthermore, preoperative hypercapnia and low BMI were predictive of reduced Cdyn.

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Table 1. Clinical characteristics of the study population

	Number (percentage) or median (range)
Age (years)	26 (8–57)
Female gender	8 (42.1%)
Body mass index (kg/m^2)	14.5 (10.1–21.0)
Indications for HSCT	
Acute myeloid leukemia	11 (57.9%)
Myelodysplastic syndrome	2 (10.5%)
Neuroblastoma	1 (5.3%)
Acute lymphoblastic leukemia	1 (5.3%)
Primary macroglobulinemia	1 (5.3%)
SCID	1 (5.3%)
Aplastic anemia	1 (5.3%)
Chediak–Higashi syndrome	1 (5.3%)
Type of transplanted stem cells	
Allogenic bone marrow	8 (42.1%)
Allogenic peripheral blood stem cells	8 (42.1%)
Allogenic cord blood	3 (15.8%)
Primary diagnosis for pulmonary complications after HSCT	
Bronchilitis obliterans	18 (94.7%)
Pulmonary fibrosis	1 (5.3%)
Interval between HSCT and respiratory symptom onset (mo)	15 (7–120)
Interval between respiratory symptom onset and LT (mo)	38 (7–137)
Type of LT	
LDLLT (bilateral / single)	10 / 4
CLT (bilateral / single)	3 / 2
Preoperative condition	
ambulatory	8 (42.1%)
NPPV	2 (10.5%)
Tracheostomy	2 (10.5%)
Pulmonary function test	
FEV_1 (% predicted)	18 (4–43)
FVC (% predicted)	36 (2–65)
FEV_1/FVC	54.9 (27.5–100.0)
Resting arterial blood gas analysis	
pH	7.36 (7.27–7.43)
$PaCO_2$	57.0 (34.0–104.0)

The pulmonary function test was not conducted preoperatively in four cases.

HSCT, hematopoietic stem cell transplantation; *SCID*, severe combined immunodeficiency; *LT*, lung transplantation; *LDLLT*, living-donor lobar lung transplantation; *CLT*, cadaveric lung transplantation; *NPPV*, noninvasive positive pressure ventilation; *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *$PaCO_2$*, partial pressure of carbon dioxide in arterial blood.

Table 2. Ventilatory and oxygenation parameters during anesthetic induction and after establishment of mechanical ventilation.

	Number (percentage) or median (range)
SpO_2 during anesthetic induction	
SpO_2 before anesthetic induction (%)	100 (95–100)
Oxygen desaturation	4 (21.1%)
Nadir SpO_2 (%)	96 (70–100)
Endotracheal tube used	
Double lumen tube	11 (57.9%)
Single lumen tube	8 (42.1%)
Ventilatory parameters after anesthetic induction	
Ventilation mode (PCV/VCV/missed)	10/4/5
PIP (cmH_2O)	26.7 (15.7–36.7)
PEEP (cmH_2O)	2.2 (0.0–5.0)
Respiratory rate (/min)	20 (10–55)
Tidal volume (ml/kg)	4.3 (1.5–7.6)
Cdyn ($ml/cmH_2O/kg$)	0.21 (0.06–0.44)
Arterial blood gas analysis after anesthetic induction	
pH	7.32 (6.96–7.50)
$PaCO_2$ (mmHg)	67.4 (35.0–192.1)
PaO_2/F_IO_2 ratio	518 (99–639)
Severe acidosis (pH < 7.2)	5 (26.3%)

Ventilation parameters were not available in five patients.

SpO_2, arterial oxygen saturation of hemoglobin; *PCV*, pressure controlled ventilation; *VCV*, volume controlled ventilation; *PIP*, peak inspiratory pressure; *PEEP*, peak end expiratory pressure; *Cdyn*, dynamic compliance; *$PaCO_2$*, partial pressure of carbon dioxide in arterial blood; *PaO_2*, partial pressure of oxygen in arterial blood; *F_IO_2*, fraction of inspired oxygen.

Table 3. Characteristics associated with oxygen desaturation during anesthetic induction.

Variable	No Oxygen desaturation (n = 15)	Oxygen desaturation (n = 4)	*P* value
Age (years)	29 (8–57)	11 (8–41)	0.064
Female gender	6 (31.6%)	2 (50.0%)	1.000
BMI (kg/m^2)	15.0 (11.1–21.0)	12.4 (10.1–19.6)	0.230
Able to ambulate preoperatively	8 (53.3%)	0 (0.0%)	0.103
Preoperative PFT			
FEV_1 (% predicted)	18 (11–43)	8 (4–27)	0.190
FVC (% predicted)	38 (12–65)	13 (2–36)	0.083
Preoperative $PaCO_2$	54.6 (34.0–77.3)	74.7 (55.8–104.0)	0.072
Cdyn	0.25 (0.11–0.44)	0.06 (0.06–0.09)	0.010
ABG analysis after anesthetic induction			
pH	7.35 (7.15–7.50)	7.12 (6.96–7.19)	0.004
$PaCO_2$	62.7 (35.0–127.3)	140.3 (104.8–192.1)	0.004
PaO_2/F_IO_2 ratio	538 (256–639)	365 (99–586)	0.317

The pulmonary function test (PFT) was not conducted preoperatively in one patient with oxygen desaturation and three patients without oxygen desaturation. Cdyn was not available in one patient with oxygen desaturation and four patients without because ventilation parameters were missing.

BMI, body mass index; *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *$PaCO_2$*, partial pressure of carbon dioxide in arterial blood; *Cdyn*, dynamic compliance; *ABG*, arterial blood gas; *PaO_2*, partial pressure of oxygen in arterial blood; *F_IO_2*, fraction of inspired oxygen.

Table 4. Characteristics associated with severe respiratory acidosis after anesthetic induction.

Variable	No severe acidosis (n = 14)	Severe acidosis (n = 5)	*P* value
Age (years)	28 (8–57)	11 (8–44)	0.210
Female gender	6 (42.9%)	2 (40.0%)	0.912
BMI (kg/m^2)	15.6 (11.1–21.0)	14.0 (10.1–19.6)	0.308
Able to ambulate preoperatively	8 (57.1%)	0 (0.0%)	0.026
Preoperative PFT			
FEV_1 (% predicted)	18 (11–43)	11 (4–27)	0.087
FVC (% predicted)	38 (15–65)	13 (2–36)	0.019
Preoperative $PaCO_2$	53.3 (34.0–77.3)	76.8 (55.8–104.0)	0.026
Cdyn	0.25 (0.11–0.44)	0.06 (0.06–0.09)	0.010
ABG analysis after			

anesthetic induction			
pH	7.35 (7.22–7.50)	7.13 (6.96–7.19)	0.001
$PaCO_2$	59.8 (35.0–103.3)	134.8 (104.8–192.1)	0.001
PaO_2/F_IO_2 ratio	541 (309–639)	273 (99–586)	0.096

The pulmonary function test (PFT) was not conducted preoperatively in one patient with severe acidosis and three patients without severe acidosis. Cdyn was not available in two patients with severe acidosis and three patients without because ventilation parameters were missing.

BMI, body mass index; *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *$PaCO_2$*, partial pressure of carbon dioxide in arterial blood; *Cdyn*, dynamic compliance; *ABG*, arterial blood gas; *PaO_2*, partial pressure of oxygen in arterial blood; *F_IO_2*, fraction of inspired oxygen.

Table 5. Multivariate linear regression analysis of dynamic compliance during mechanical ventilation.

Variables	Regression coefficient	95% CI	*P* value
Preoperative $PaCO_2$ (mmHg)	−0.004	−0.007 to −0.001	0.006
BMI (kg/m^2)	0.014	0.0001 to 0.030	0.049

Five patients were excluded from analysis because their Cdyn value was not available.

$PaCO_2$, partial pressure of carbon dioxide in arterial blood; *BMI*, body mass index; *CI*, confidence interval.

Figure legends

Figure 1. Bivariate linear correlation between dynamic compliance (Cdyn) after establishment of mechanical ventilation and preoperative partial pressure of carbon dioxide in arterial blood [$PaCO_2$] (**a**), body mass index (**b**), forced expiratory volume in 1 s [FEV_1] (**c**), and forced vital capacity [FVC] (**d**). Five patients were excluded from analysis because their Cdyn values were not available. The pulmonary function test was not conducted in three patients.