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ORIGINAL ARTICLE

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

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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 anesthetic induction ($p = 0.01$). 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.
Conclusions 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.

Keywords Lung transplantation · Hematopoietic stem cell transplantation (HSCT) · Anesthesia · Dynamic compliance · Oxygen desaturation

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.

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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 1 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 seven 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 patients except for one 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

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	
Bronchiolitis 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

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 per minute) 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

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 (per minute)	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

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. Inability 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 (Fig. 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 5).

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

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

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

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	0.0001–0.030	0.049

Five patients were excluded from analysis because their Cdyn values were not available

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

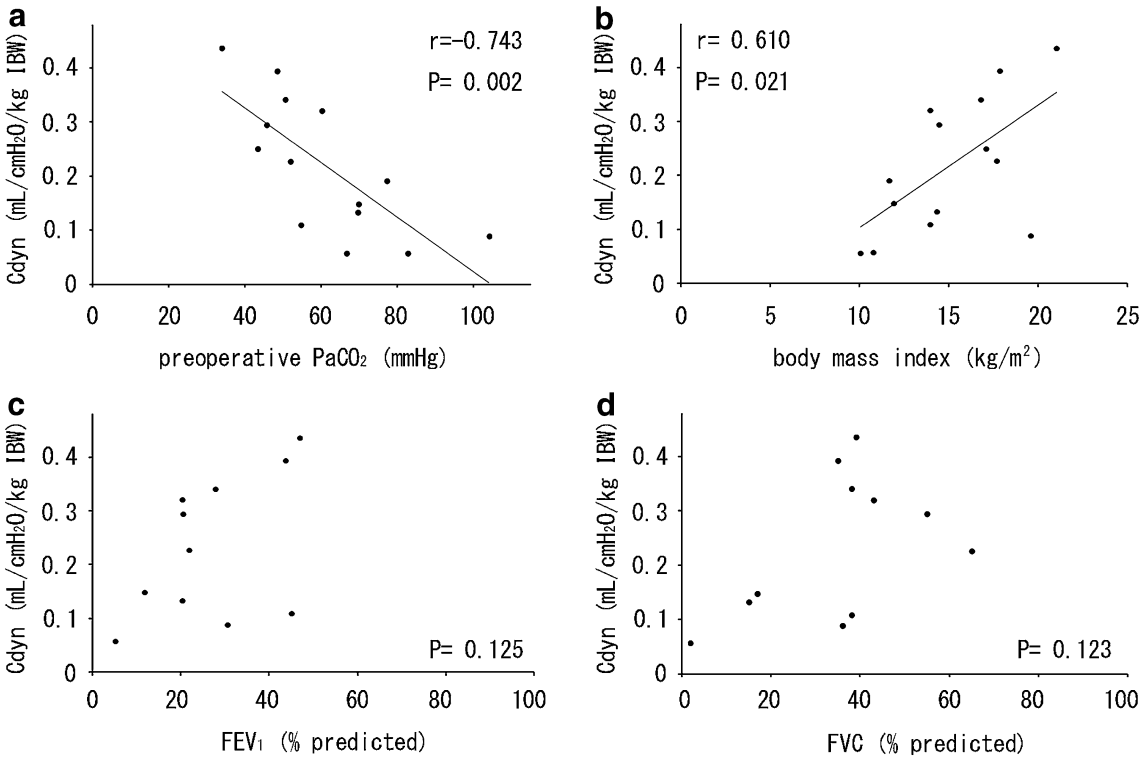

Fig. 1 Bivariate linear correlation between dynamic compliance (Cdyn) after establishment of mechanical ventilation and preoperative partial pressure of carbon dioxide in arterial blood [$PaCO_2$] (**a**), body mass index (**b**), forced expiratory volume in 1 s [FEV_1] (**c**), and forced vital capacity [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

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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