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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 10^{th} and the 90^{th} 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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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.

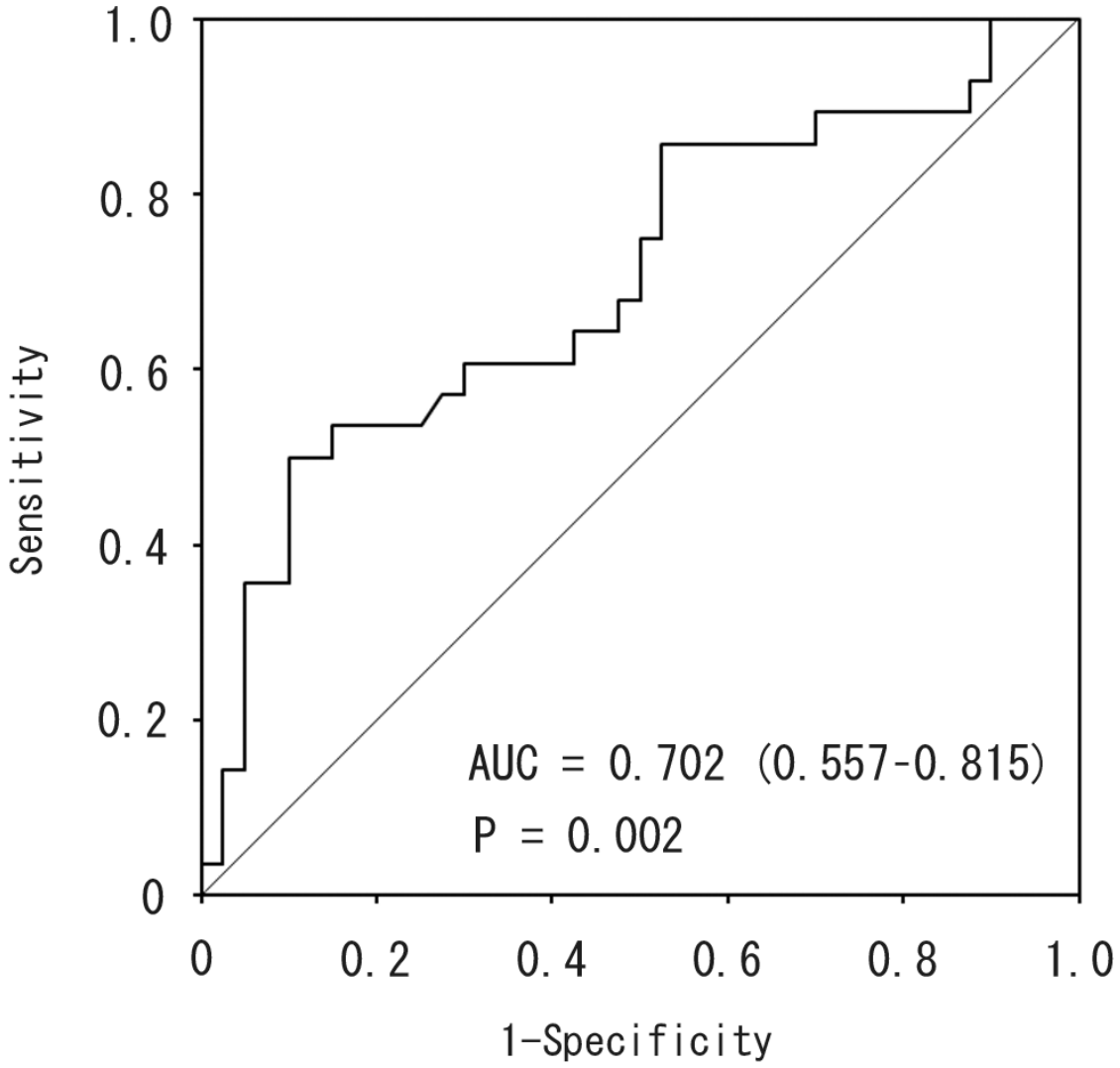

Table 1. Preoperative characteristics of the study population (n = 68)

	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
%FEV1	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; FEV1, 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