Surgery Today (2019) 49:571–579
https://doi.org/10.1007/s00595-019-1770-z

ORIGINAL ARTICLE

Lung-diffusing capacity for carbon monoxide predicts early complications after cardiac surgery

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Received: 7 August 2018 / Accepted: 3 January 2019 /

Abstract

Purpose Preoperative pulmonary dysfunction has been associated with increased operative mortality and morbidity after cardiac surgery. This study aimed to determine whether values for the diffusing capacity of the lung for carbon monoxide (DL_{CO}) could predict postoperative complications after cardiac surgery.

Methods This study included 408 consecutive patients who underwent cardiac surgery between June 2008 and December 2015. DL_{CO} was routinely determined in all patients. A reduced DL_{CO} was clinically defined as $\%DL_{CO} < 70\%$. $\%DL_{CO}$ was calculated as DL_{CO} divided by the predicted DL_{CO}. The association between $\%DL_{CO}$ and in-hospital mortality was assessed, and independent predictors of complications were identified by a logistic regression analysis.

Results Among the 408 patients, 338 and 70 had $\%DL_{CO}$ values of $\geq 70\%$ and $< 70\%$, respectively. Complications were associated with in-hospital mortality ($P < 0.001$), but not $\%DL_{CO}$ ($P = 0.275$). A multivariate logistic regression analysis with propensity score matching identified reduced DL_{CO} as an independent predictor of complications (OR, 3.270; 95%CI, 1.356–7.882; $P = 0.008$).

Conclusions $\%DL_{CO}$ is a powerful predictor of postoperative complications. The preoperative DL_{CO} values might provide information that can be used to accurately predict the prognosis after cardiac surgery.

Clinical trial registration number UMIN000029985.

Keywords Cardiac surgery · Diffusing capacity of lung for carbon monoxide · Complication

Introduction

Preoperative pulmonary dysfunction in chronic obstructive pulmonary disease (COPD) has been considered to be associated with increased operative mortality and morbidity after cardiac surgery. A careful evaluation of the pulmonary function before and after cardiac surgery demonstrated a significant reduction in lung volume, diffusion capacity, and oxygenation at 2 weeks after surgery, with partial improvement after 4 months [1]. The preoperative identification of patients who are at greater risk of developing complications is important to prevent postoperative complications and obtain a good operative outcome.

The analysis of the diffusing capacity of the lung for carbon monoxide (DL_{CO}) is a clinically useful pulmonary function test (PFT). Unlike other spirometric measurements, DL_{CO} is less influenced by patient effort [2]. DL_{CO} represents the ability of the lung to diffuse carbon monoxide across its membranes and assesses the transfer of gases from the alveoli to red blood cells. The diffusion of O_2 depends on the following factors: the alveolar ventilation/capillary perfusion ratio, which establishes the partial pressure gradient of O_2 between the alveoli and plasma; the physical characteristics of the alveolar–capillary interface; the capillary blood volume available for gas exchange; the hemoglobin (Hb) concentration; and the reaction rate between O_2 and Hb [3, 4]. The diffusion characteristics of the lung are commonly assessed by tests of CO transfer. CO diffuses across the alveoli and binds to Hb with 240-fold greater affinity than O_2 [3]. DL_{CO} depends on two resistances arranged in series according to the following equation:

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$1/\mathrm{DL_{CO}} = 1/\mathrm{D_M} + 1/\theta_{CO}\ V_C$ [3–5], where D_M is the alveolar–capillary membrane conductance, θ_{CO} is the rate of CO uptake by the whole blood combined with Hb measured in vitro, and V_C is the lung capillary blood volume [3–5]. A decline in $\mathrm{DL_{CO}}$ can occur as a result of destruction of alveolar structures, distal airway dysfunction, contraction of the pulmonary capillary volume due to ventilation, perfusion abnormalities, and Hb abnormalities.

$\mathrm{DL_{CO}}$ is an equally powerful predictor of postoperative complications in patients with and without COPD after lung resection. A previous study suggested that $\mathrm{DL_{CO}}$ should be routinely measured during preoperative evaluations, regardless of whether a patient's spirometric values are abnormal [2].

Another study reported that reduced alveolar–capillary membrane conductance is associated with pulmonary congestion [6]. Thus, $\mathrm{DL_{CO}}$ may be influenced by pulmonary edema and fluid accumulation in the interstitial spaces before and after cardiac surgery. The present study aimed to determine whether $\mathrm{DL_{CO}}$ can serve as a predictor of complications arising after cardiac surgery.

Patients and methods

Patients

The study protocol was approved by the Institutional Review Board of the Dokkyo Medical University. Between June 2008 and December 2015, 2040 patients underwent cardiac surgery at Dokkyo Medical University Hospital. A total of 408 patients in whom preoperative $\mathrm{DL_{CO}}$ values were routinely collected within 1 week before scheduled cardiac surgery were included in this study. The attending physician for each patient made the decision to proceed with the PFT, which included measurement of $\mathrm{DL_{CO}}$, based on clinical indications. The exclusion criteria were any emergency or urgent operation, aortic surgery, beating heart surgery, and approaches other than median sternotomy. We reviewed the medical records of the patients, including the demographics, preoperative clinical data, PFT findings, hemodynamic data from cardiac catheterization, and operative and postoperative data.

$\mathrm{DL_{CO}}$ measurement and $\%\mathrm{DL_{CO}}$

We measured $\mathrm{DL_{CO}}$ in a single-breath-hold maneuver with the patient seated upright in a chair with their nostrils closed with a clip. The patients then breathed normally and exhaled to residual volume, and then, a carbon monoxide–helium mixture was forcefully inhaled to total lung capacity, and held for 10 s and then exhaled. The patients exhaled to wash out the estimated mechanical and anatomical dead space. Alveolar samples were then collected, and $\mathrm{DL_{CO}}$ was calculated from the total volume of the lung, breath-hold duration, and the initial and final alveolar concentrations of CO. The exhaled helium concentration was used to determine a single-breath estimate of the total lung capacity and the initial alveolar concentration of CO. The predicted $\mathrm{DL_{CO}}$ was determined from regression equations according to age, height, and sex (predicted $\mathrm{DL_{CO}}$ for men, $15.5\times$ body surface area (BSA) $- 0.23\times$ age $+ 6.8$; predicted $\mathrm{DL_{CO}}$ for women, $15.5\times\mathrm{BSA} - 0.117\times$ age $+ 0.5$) [7]. $\%\mathrm{DL_{CO}}$ was calculated by dividing the actual $\mathrm{DL_{CO}}$ by the predicted $\mathrm{DL_{CO}}$.

Surgical technique

A median sternotomy approach was applied under general anesthesia to all patients. Cardiopulmonary bypass (CPB) was established through the ascending aorta or by right atrial or bicaval cannulation. The myocardium was protected by antegrade and retrograde cardioplegia with intermittent cold-blood cardioplegia and reperfusion with warm-blood cardioplegia. A normothermic temperature was maintained during CPB. The patients were transferred to the intensive care unit immediately after the procedure with ventilator assistance and monitoring.

Definitions of complications

Postoperative outcomes were defined according to the Society of Thoracic Surgeons National Database as follows. In-hospital death was defined as the death of a patient due to any cause during hospitalization in the institution, where they underwent cardiac surgery. Stroke was defined as a central neurologic deficit persisting for > 72 h. Wound infection was defined as infection involving subcutaneous tissue, muscle, bone, or the mediastinum, and requiring surgical intervention. Respiratory complications were also included. The incidence of postoperative respiratory complications was scored on an ordinal scale of 1–4, using the operational definitions of postoperative pulmonary complications described by Kroenke et al. [8] (Table 1) . Clinically significant respiratory complications were defined as one item among grade 3 or 4 complications.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation (SD) and were compared using Student's *t* test or the Mann–Whitney test, as appropriate. Nominal variables are expressed as percentages and were analyzed using the χ^2 test or Fisher's exact probability test. All variables with *P* values of < 0.20 in the univariate analysis were included in the multivariable analyses. Other clinically relevant

Table 1 Operational definitions of postoperative pulmonary complications

Grade	Definition
1	Cough, dry Microatelectasis: abnormal lung findings and temperature > 37.5 °C without other documented cause; results of chest radiograph either normal or unavailable Dyspnea, not due to other documented cause
2	Cough, productive, not due to other documented cause Bronchospasm: new wheezing or pre-existent wheezing resulting in change of therapy Hypoxemia: alveolar–arterial gradient > 29 and symptoms of dyspnea or wheezing Atelectasis: radiological confirmation plus either temperature > 37.5 °C or abnormal lung findings Hypercarbia, transient, requiring treatment, such as naloxone or increased manual or mechanical ventilation as an adverse reaction to pulmonary medication
3	Pleural effusion, resulting in thoracentesis Pneumonia, suspected: radiological evidence without bacteriological confirmation Pneumonia, proved: radiological evidence and documentation of pathological organism by Gram stain or culture Pneumothorax Re-intubation postoperatively or intubation, period of ventilator dependence does not exceed 48 h
4	Ventilatory failure: postoperative ventilator dependence exceeding 48 h, or re-intubation with subsequent period of ventilator dependence exceeding 48 h

variables, namely, sex, age, body mass index (BMI), and BSA, were adjusted in the multivariable analysis. Independent predictors of postoperative complications after cardiac surgery were identified using a multivariate logistic regression model with the forced entry method. Odds ratios (OR), 95% confidence intervals (95%CI), and *P* values are reported. To minimize selection bias derived from the retrospective observational study design, propensity score analyses were performed to generate two groups, considering the following covariates: age, sex, BMI, %VC, and hemoglobin. 70 patients with $\%DL_{CO} < 70\%$ and 67 patients with $\%DL_{CO} \geq 70\%$ were matched. A logistic regression analysis for the abovementioned covariates, with nearest-neighbor one-to-one matching, was performed to determine the propensity scores. All statistical tests were two-sided, and *P* values of < 0.05 were considered to indicate statistical significance. All statistical analyses were performed using the IBM SPSS statistics 24 software program (IBM, Armonk, NY, USA).

Results

Patient characteristics and outcomes

Table 2 summarizes the characteristics of the 408 patients (age, 66.0 ± 10.0 years; male, $n = 295$ [72.3%]), whose data were analyzed in this study. Isolated coronary artery bypass grafting (CABG) was performed for 224 (54.9%) patients, and 184 (45.9%) underwent valve surgery (including concomitant cardiac surgery). Six (1.47%) patients died in hospital due to multi-organ failure ($n = 1$), sudden death ($n = 1$), and sepsis ($n = 4$). Operative complications developed in 91 (22.3%) patients and consisted of gastrointestinal disorder ($n = 3$), stroke ($n = 4$), renal disorder ($n = 5$), cardiac disorder ($n = 7$), wound infection ($n = 19$), and respiratory complications ($n = 71$; Grade 3: $n = 61$, Grade 4: $n = 3$). Figures 1 and 2 show the relationship between patients with all complications or respiratory complications and $\%DL_{CO}$ by quartile. The incidence of all complications significantly differed in Q1 (OR, 3.323; 95%CI, 1.472–7.500; $P = 0.005$); the OR for respiratory complications was 3.462 (95%CI, 1.434–8.357; $P = 0.005$). Although a DLco value of < 80% of the predicted value was considered abnormal, according to a previous definition by Steenhuis et al. [9], the incidence of complications differed in Q1 (%DLco < 74.6%). A DLco value of < 70% the predicted value was considered to be the cut-off value. The area under the receiver operating characteristic curve values was 0.625 (95%CI 0.558–0.692) for all complications and 0.632 (95%CI 0.557–0.707) for respiratory complications. The sensitivity and specificity of %DLco, with a cut-off value of 70%, were 0.864 and 0.297, respectively, for all complications (0.861 and 0.324 for respiratory complications).

Preoperative demographics and clinical variables according to the $\%DL_{CO}$ risk

Table 2 shows the preoperative and perioperative factors of patients with $\%DL_{CO}$ of ≥ 70% ($n = 338$) or < 70% ($n = 70$). Significant differences were observed in age (66.5 ± 9.70 vs. 63.8 ± 11.2 years; $P = 0.036$) and sex (female) (86 [25.4%] vs. 27 [38.6%]; $P = 0.025$). There were no significant differences in the risk factors, which included hypertension, hyperlipidemia, history of smoking, BMI, BSA, and HbA_{1C}. Among the clinical and biochemical parameters, significant differences were observed in extracardiac arteriopathy (52 [15.4%] vs. 21 [30.0%]; $P = 0.004$) and Hb (13.1 ± 1.7 vs.

Table 2 Demographics and clinical variables stratified by $\%DL_{CO}$ risk

	All patients ($n=408$)	$\%DL_{CO} \geq 70\%$ ($n=338$)	$\%DL_{CO} < 70\%$ ($n=70$)	P
Female, *n* (%)	113 (27.7)	86 (25.4)	27 (38.6)	0.025
Age (years)	66 ± 10.0	66.5 ± 9.7	63.8 ± 11.2	0.036
BMI (kg/m^2)	23.6 ± 3.5	23.6 ± 3.5	23.3 ± 3.4	0.412
BSA (m^2)	1.64 ± 0.19	1.64 ± 0.19	1.62 ± 0.19	0.413
Hypertension, *n* (%)	330 (80.9)	276 (81.7)	54 (77.1)	0.382
Hyperlipidemia, *n* (%)	264 (64.7)	219 (64.8)	45 (64.3)	0.936
Smoking, *n* (%)	264 (64.7)	213 (63.0)	51 (72.9)	0.117
Hemoglobin A_{1C}, (%)	6.0 (1.0)	6.0 (0.9)	6.2 (1.3)	0.113
NYHA class (I, II), *n* (%)	332 (81.4)	275 (81.4)	57 (81.4)	0.382
Recent AMI, *n* (%)	17 (4.2)	14 (4.1)	3 (4.3)	0.956
Atrial fibrillation, *n* (%)	79 (19.4)	64 (18.9)	15 (21.4)	0.631
Ex. arteriopathy, *n* (%)	73 (17.9)	52 (15.4)	21 (30.0)	0.004
EF (%)	57.4 ± 13.7	57.7 ± 13.7	56.0 ± 14.0	0.345
BNP (pg/mL)	205.93 ± 403.7	193.6 ± 381.3	265.3 ± 497.1	0.023*
%VC (%)	94.6 ± 16.3	95.6 ± 16.1	89.6 ± 16.5	0.005
$FEV_{1.0}\%$ (%)	72.6 ± 10.6	72.6 ± 10.1	72.4 ± 12.6	0.878
PaO_2 (mmHg)	89.1 ± 13.2	89.2 ± 2.9	88.5 ± 14.8	0.690
$PaCO_2$ (mmHg)	39.7 ± 3.9	39.8 ± 3.9	39.2 ± 4.3	0.328
Hemoglobin (g/dL)	13.0 ± 1.8	13.1 ± 1.7	12.3 ± 1.9	< 0.001
Creatinine (mg/dL)	1.3 ± 1.7	1.3 ± 1.7	1.3 ± 1.7	0.306*
Euro score II	2.05 ± 1.80	1.99 ± 1.75	2.34 ± 1.99	0.051*
STS score	2.25 ± 2.77	2.21 ± 2.73	2.48 ± 2.98	0.516*
CABG only, *n* (%)	224 (54.9)	193 (57.1)	31 (44.3)	0.050
Operative time (min)	324.2 ± 80.2	322.5 ± 79.2	332.3 ± 85.3	0.350
Pump time (min)	145.7 ± 50.2	144.3 ± 49.9	152.0 ± 51.5	0.244
Aortic clamp time (min)	105.97 ± 42.3	105.0 ± 42.6	110.2 ± 40.5	0.347
All complications, *n* (%)	91 (22.3)	64 (18.9)	27 (38.6)	< 0.001
Resp. complication, *n* (%)	71 (17.4)	48 (14.2)	23 (32.9)	< 0.001
Hospital mortality, *n* (%)	6 (1.5)	4 (1.2)	2 (2.9)	0.275

Continuous data are presented as mean ± SD

BMI body mass index, *BNP* brain natriuretic peptide, *BSA* body surface area, *CABG* coronary artery bypass graft, *EF* ejection fraction, *Ex.* arteriopathy extracardiac arteriopathy, $FEV_{1.0}\%$ percent predicted forced expiratory volume in 1 s, *NYHA* New York Heart Association, *%VC* percent predicted vital capacity, Recent *AMI* acute myocardial infarction within 3 months, *Resp* respiratory, *ST,S* Society of Thoracic Surgeons, $\%DL_{CO}$ percent predicted diffusing capacity of lung for carbon monoxide

*Fisher exact test or Mann–Whitney test

12.3 ± 1.9 g/dL; $P<0.001$). In terms of the cardiac function, the brain natriuretic peptide (BNP) levels of the two groups were significantly different (193.6 ± 381.3 vs. 265.3 ± 497.1 pg/mL; $P=0.023$), whereas ejection fraction was not (57.7% ± 13.7% vs. 56.0% ± 14.0%; $P=0.345$). Among the factors associated with the respiratory function, %VC was significantly different (95.65 ± 16.1% vs. 89.6 ± 16.5%; $P=0.005$), whereas $FEV_{1.0}\%$ was not (72.6 ± 10.1% vs. 72.4 ± 12.6%; $P=0.878$). Among the factors associated with the renal function, the serum creatinine level did not differ to a statistically significant extent (1.3 ± 1.7 vs. 1.3 ± 1.7 mg/dL; $P=0.306$).

CABG was the only operative method for which there was significant difference (193 [57.1%] vs. 31 [44.3%] $P=0.050$). The operative time (322.5 ± 79.2 vs. 323 ± 85.3 min; $P=0.350$), pump time (144.3 ± 49.9 vs. 152.0 ± 51.5 min; $P=0.244$), and aortic clamp time (105.0 ± 22.6 vs. 110.2 ± 40.5 min; $P=0.347$) did not differ to a statistically significant extent. Furthermore, there was no significant difference in the rate of hospital mortality (4 [1.2%]) vs. 2 [2.9%]; $P=0.275$. There were significant differences between the two groups in the rates of all complications (64 [18.9%] vs. 27 [38.6%]; $P<0.001$) and respiratory complications (48 [14.2%] vs. 23 [32.9%]; $P<0.001$).

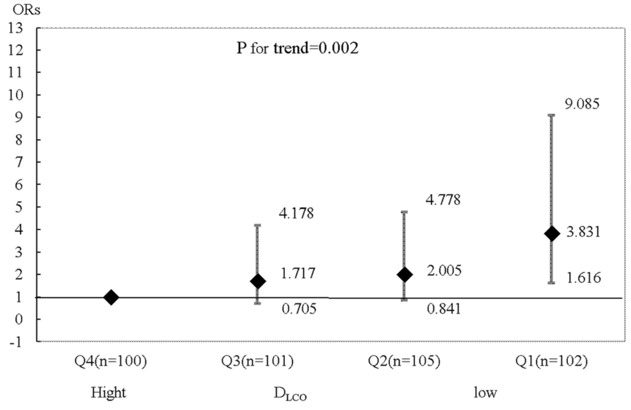

Fig. 1 Patients with all complications after surgery and the %DL_{CO} quartiles. The %DL_{CO} quartiles were as follows: Q1 (≤ 74.6%), Q2 (74.7–88.8%), Q3 (88.9–101.7%), and Q4 (≥ 101.8%). *DL_{CO}* diffusing capacity of lung for carbon monoxide, *OR* odds ratio. Error bars represent 95% confidence intervals. OR adjusted for sex, age, body mass index, body surface area, hemoglobin A_{1C}, New York Heart Association class, atrial fibrillation, brain natriuretic peptide, %vital capacity, hemoglobin, logistic Euro score II, STS score, durations of surgery, pump, and aortic clamp

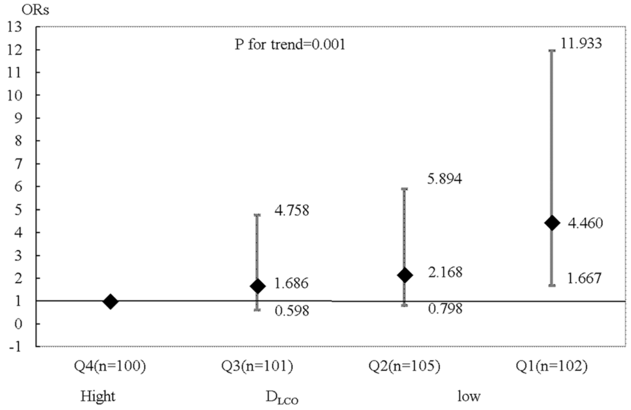

Fig. 2 Patients with respiratory complications after surgery and the %DL_{CO} quartiles. The %DL_{CO} quartiles were as follows: Q1 (≤ 74.6%), Q2 (74.7–88.8%), Q3 (88.9–101.7%), and Q4 (≥ 101.8%). The ORs were adjusted as described in the Fig. 1 legend. *DL_{CO}* diffusing capacity of lung for carbon monoxide, *OR* odds ratio. Error bars represent 95% confidence intervals

%DL_{CO} as a predictor of complications after cardiac surgery

Table 3 shows the results of the univariate analysis of patients with all complications and those with respiratory complications. Among the preoperative data, significant differences were observed in the rates of %DL_{CO} < 70%, BNP ≥ 100 pg/mL, Hb < 11 g/dL, and the Euro Score II and STS score values of the patients with and without all and those with and without respiratory complications. Among the perioperative factors, significant differences were observed in the operative time, the pump time and the aortic clamp time between the patients with and without complications. A multivariate logistic regression analysis identified BMI (OR, 1.156; 95%CI, 1.039–1.286; $P = 0.008$), BSA (OR, 0.040; 95%CI, 0.003–0.575; $P = 0.018$), and a reduced %DL_{CO} (OR, 2.682; 95%CI, 1.449–4.962; $P = 0.002$) as preoperative factors that were significant independent predictors of all complications. Pump time (OR, 1.016; 95%CI, 1.003–1.030; $P = 0.017$) as identified as a perioperative factor that was a significant predictor of all complications (Table 4). The multivariate logistic regression analysis identified a reduced %DL_{CO} (OR, 2.833; 95%CI, 1.490–5.398; $P = 0.001$) and increased HbA_{1C} (OR, 2.284; 95%CI. 1.102–4.733; $P = 0.026$) as preoperative factors that were significant independent predictors of respiratory complications (Table 5). The propensity score analysis identified a reduced %DL_{CO} as a predictor of all complications and respiratory complications: all complications (OR, 3.270; 95%CI, 1.356–7.882; $P = 0.008$) and respiratory complications (OR, 3.447; 95%CI, 1.343–8.846; $P = 0.010$) (Table 6).

Discussion

The principal finding of this study was that the preoperative DL_{CO} was correlated with postoperative complications after cardiac surgery. Others have described significant and prolonged impairment of the pulmonary function after cardiac surgery [1]. Decreased ventilation, pulmonary disease, and reduced alveolar perfusion caused by poor cardiac output and chronic heart failure might also influence DL_{CO} [10]. DL_{CO} is a clinically useful indicator of the lung function, because it assesses gas transfer from the alveoli to the red blood cells. The preoperative DL_{CO} is not routinely measured in patients in most cardiac surgery units. Reduced postoperative capillary filtration due to basal membrane thickening, enhanced alveolar fluid clearance, and increased lymphatic drainage leads to restricted lung spirometry and impaired gas transfer [6]. We hypothesized that the postoperative DL_{CO} might be more decreased than the preoperative DL_{CO} and that this could serve as a predictor of early complications after cardiac surgery. The present study found that more postoperative complications developed among patients with %DL_{CO} of < 70% than among those with %DL_{CO} of > 70%. A previous study also found that patients with stable chronic heart failure had decreased %VC values, in addition to decreased DL_{CO} and D_M values [11]. The present study showed that the %VC values were decreased and the BNP levels were increased in patients with lower DL_{CO} values; however, these patients might have had preoperative chronic heart failure. Thus, %DL_{CO} might be a marker of heart failure.

Table 3 Demographics of patients and the clinical variables according to complications

	All complications		*P*	Respiratory complications		*P*
	Absent (*n* = 317)	Present (*n* = 91)		Absent (*n* = 337)	Present (*n* = 71)	
Sex, female, *n* (%)	85 (26.8)	28 (30.8)	0.457	89 (26.4)	24 (33.8)	0.206
Age ≥ 75 years, *n* (%)	62 (19.6)	20 (22.0)	0.612	65 (19.3)	17 (23.9)	0.374
BMI (kg/m^2)	23.6 ± 3.4	23.6 ± 3.8	0.912	23.6 ± 3.4	23.4 ± 3.8	0.610
BSA (m^2)	1.64 ± 0.2	1.61 ± 0.09	0.147	1.64 ± 0.19	1.6 ± 0.19	0.069
Hypertension, *n* (%)	255 (80.4)	75 (82.4)	0.673	272 (80.7)	58 (81.7)	0.849
Hyperlipidemia, *n* (%)	208 (65.6)	56 (61.5)	0.473	221 (65.6)	43 (60.6)	0.442
Smoking, *n* (%)	202 (63.7)	62 (68.1)	0.438	219 (65.0)	45 (63.4)	0.797
Hemoglobin A1c ≥ 7%, *n* (%)	45 (14.4)	19 (21.1)	0.123	47 (14.2)	17 (23.9)	0.041
NYHA grade > III, *n* (%)	54 (17.0)	22 (24.2)	0.123	58 (17.2)	18 (25.4)	0.109
Recent AMI, *n* (%)	15 (4.7)	2 (2.2)	0.286	15 (4.5)	2 (2.8)	0.531
Atrial fibrillation, *n* (%)	56 (17.7)	23 (25.3)	0.105	60 (17.8)	19 (26.8)	0.083
Ex. arteriopathy, *n* (%)	57 (18.0)	16 (17.6)	0.930	60 (17.8)	13 (18.3)	0.920
EF < 40%, *n* (%)	35 (11.0)	13 (14.3)	0.397	38 (11.3)	10 (14.1)	0.504
BNP ≥ 100 pg/mL, *n* (%)	140 (44.7)	54 (60.0)	0.011	152 (45.8)	42 (59.2)	0.041
$\%DL_{CO} < 70\%$, *n* (%)	43 (13.6)	27 (29.7)	< 0.001	47 (13.9)	23 (32.4)	< 0.001
%VC < 80%, *n* (%)	45 (14.2)	20 (22.0)	0.074	50 (14.8)	15 (21.1)	0.188
$FEV_{1.0}\% < 75\%$, *n* (%)	158 (49.8)	43 (47.3)	0.663	167 (49.6)	34 (47.9)	0.798
$PaO_2 < 80$ mmHg, *n* (%)	69 (23.3)	16 (18.8)	0.381	72 (22.9)	13 (19.7)	0.575
$PaCO_2 \geq 40$ mmHg, *n* (%)	147 (49.7)	39 (45.9)	0.539	157 (49.8)	29 (43.9)	0.383
Hemoglobin, < 11 g/dL, *n* (%)	36 (11.4)	19 (20.9)	0.019	40 (11.9)	15 (21.1)	0.038
Creatinine ≥ 2.0 mg/dL, *n* (%)	23 (7.3)	9 (9.9)	0.410	26 (7.7)	6 (8.5)	0.834
Euro Score II	1.90 ± 1.58	2.59 ± 2.34	0.001*	1.91 ± 1.57	2.72 ± 2.53	0.003*
STS score	2.04 ± 2.51	3.01 ± 3.44	0.002*	2.09 ± 2.57	3.06 ± 3.49	0.006*
CABG alone, *n* (%)	178 (56.2)	46 (50.5)	0.344	188 (55.8)	36 (50.7)	0.434
Operative time (min)	318.7 ± 79.8	343.1 ± 79.4	0.010	320.5 ± 79.6	341.5 ± 81.6	0.045
Pump time (min)	140.7 ± 45.2	163 ± 61.9	0.002	142.3 ± 45.7	161.7 ± 65.9	0.020
Aortic clamp time (min)	103 ± 38.8	116.2 ± 51.4	0.025	104 ± 39.4	115.2 ± 53.1	0.094

Continuous data are presented as mean ± SD

BMI body mass index, *BNP* brain natriuretic peptide, *BSA* body surface area, *CABG* coronary artery bypass graft, *EF* ejection fraction, *Ex.* arteriopathy extracardiac arteriopathy, $FEV_{1.0}\%$ percent predicted forced expiratory volume in 1 s, *NYHA* New York Heart Association, *%VC* percent predicted vital capacity, Recent *AMI* acute myocardial infarction within 3 months, *Resp* respiratory, *STS* Society of Thoracic Surgeons, $\%DL_{CO}$ percent predicted diffusing capacity of lung for carbon monoxide

*Fisher exact test or Mann–Whitney test

A previous study suggested that cardiac surgery may also contribute to a greater reduction in DL_{CO}. The mechanism underlying the reduction of DL_{CO} after cardiac surgery is unclear. One hypothesis is that it might reflect pathophysiological changes in the pulmonary microcirculation initiated by CPB, such as a systemic inflammatory response with coagulopathy and altered microvascular permeability [12]. That CPB interferes with pulmonary function has been established. It can induce adverse effects on alveolar stability by activating the complement cascade, sequestering neutrophils in the pulmonary microvascular bed, releasing oxygen-derived free radicals, and changing the composition of alveolar surfactant [13]. The mechanism underlying the diffusion impairment after cardiac surgery could be caused by pulmonary edema and the accumulation of fluid in interstitial spaces, ventilation–perfusion mismatches, or changes in Hb concentrations [14]. A few studies have identified a relationship between DL_{CO} and the outcomes after cardiac surgery. Published data show that a $\%DL_{CO}$ value of < 50% the predicted value at the preoperative PFT is an independent risk factor for a > threefold increase in mortality after adjustment for mortality risk estimates [15]. Few patients in the present study had a $\%DL_{CO}$ value of < 50%. Thus, our analysis included $\%DL_{CO} < 70\%$ as an approximation for Q1. The findings of the present study showed that $\%DL_{CO} < 70\%$ in a preoperative PFT was independently associated with a > 3.3-fold increase in

Table 4 Univariate and multivariate analyses of the predictors of all complications

	Univariate analysis			Multivariate analysis		
	OR	(95%CI)	*P*	OR	(95%CI)	*P*
Sex (female)	1.213	(0.729–2.020)	0.458	0.463	(0.199–1.076)	0.074
Age (≥ 75 years)	1.159	(0.656–2.046)	0.612	0.745	(0.354–1.566)	0.438
BMI (kg/m^2)	1.004	(0.939–1.073)	0.917	1.156	(1.039–1.286)	0.008
BSA (m^2)	1.034	(0.933–1.147)	0.148	0.040	(0.003–0.575)	0.018
Hemoglobin A1c (≥ 7%)	1.539	(0.859–2.758)	0.147	1.744	(0.872–3.4862)	0.116
NYHA class (III, IV)	0.594	(0.878–2.743)	0.126	1.520	(0.794–2.909)	0.206
Atrial fibrillation	1.576	(0.906–2.743)	0.107	1.338	(0.660–2.714)	0.420
BNP (≥ 100 pg/mL)	1.854	(1.150–2.986)	0.011	1.091	(0.614–1.940)	0.767
$\%\mathrm{DL}_{\mathrm{CO}}$ (< 70%)	2.688	(1.547–4.673)	< 0.001	2.682	(1.449–4.962)	0.002
%VC (< 80%)	1.703	(0.946–3.065)	0.076	1.243	(0.620–2.491)	0.540
Hemoglobin (< 11 g/dL)	2.060	(1.116–3.803)	0.021	1.306	(0.623–2.735)	0.479
Euro score II	1.204	(1.069–1.056)	0.002	1.028	(0.857–1.233)	0.763
STS score	1.113	(1.033–1.200)	0.005	1.080	(0.964–1.211)	0.185
Operative time (min)	1.004	(1.001–1.006)	0.012	0.999	(0.995–1.004)	0.752
Pump time (min)	1.008	(1.004–1.013)	< 0.001	1.016	(1.003–1.030)	0.017
Aortic clamp time (min)	1.007	(1.002–1.012)	0.01	0.988	(0.975–1.002)	0.085

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *BNP* brain natriuretic peptide, *BSA* body surface area, *NYHA* New York Heart Association, *%VC* percent predicted vital capacity, *STS* Society of Thoracic Surgeons, $\%DL_{CO}$ percent predicted diffusing capacity of lung for carbon monoxide

Table 5 Univariate and multivariate analyses of predictors of respiratory complications

	Univariate analysis			Multivariate analysis		
	OR	(95%CI)	*P*	OR	(95%CI)	*P*
Sex (female)	1.423	(0.822–2.462)	0.207	0.587	(0.239–1.440)	0.245
Age (≥ 75 years)	1.317	(0.717–2.421)	0.375	0.942	(0.429–2.068)	0.882
BMI (kg/m^2)	1.002	(0.591–1.77)	0.941	1.099	(0.979–1.233)	0.108
BSA (m^2)	0.278	(0.070–1.109)	0.070	0.062	(0.003–1.096)	0.058
HbA1c (≥ 7%)	1.910	(1.020–3.571)	0.043	2.284	(1.102–4.733)	0.026
NYHA class (III, IV)	1.634	(0.892–2.991)	0.112	1.512	(0.751–3.261)	0.246
Atrial fibrillation	1.687	(0.930–3.058)	0.085	1.516	(0.705–3.261)	0.287
BNP (≥ 100 pg/mL)	1.720	(1.020–2.885)	0.042	0.962	(0.514–1.802)	0.904
$\%\mathrm{DL}_{\mathrm{CO}}$ (< 70%)	2.960	(1.647–5.306)	< 0.001	2.833	(1.490–5.388)	0.001
%VC (< 80%)	1.537	(0.807–2.928)	0.191	1.022	(0.475–2.196)	0.956
Hemoglobin (< 11 g/dL)	1.989	(1.029–3.842)	0.041	1.356	(0.621–2.963)	0.445
Euro score II	1.226	(1.084–1.088)	0.001	1.059	(0.876–1.281)	0.553
STS score	1.106	(1.024–1.195)	0.011	1.044	(0.922–1.182)	0.498
Operative time (min)	1.003	(1.000–1.006)	0.047	0.999	(0.994–1.004)	0.703
Pump time (min)	1.007	(1.002–1.032)	0.004	1.013	(0.999–1.028)	0.066
Aortic clamp time (min)	1.006	(1.000–1.012)	0.043	0.990	(0.976–1.004)	0.168

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *BNP* brain natriuretic peptide, *BSA* body surface area, *NYHA* New York Heart Association, *%VC* percent predicted vital capacity, *STS* Society of Thoracic Surgeons, $\%DL_{CO}$ percent predicted diffusing capacity of lung for carbon monoxide

risk for all complications after adjustment for morbidity risk estimates; the risk of respiratory complications was increased > 3.4-fold.

Postoperative respiratory complications continue to affect patient morbidity and mortality, length of hospital stay, and overall resource utilization, despite advances in preoperative, intraoperative. and postoperative care [16–18]. Respiratory muscle dysfunction due to surgery can lead to a reduced vital capacity, tidal volume, and total lung capacity [19]. This could cause atelectasis in the basal lung segments

Table 6 Propensity score analyses of predictors of all and respiratory complications

	All complications			Respiratory complications		
	OR	(95% CI)	*P*	OR	(95% CI)	*P*
BSA (m^2)	0.446	(0.040–4.943)	0.511	0.273	(0.021–3.504)	0.319
HbA1c ($\geq 7\%$)	0.577	(0.149–2.241)	0.427	0.959	(0.245–3.763)	0.953
NYHA class (III,IV)	2.416	(0.797–7.322)	0.119	1.965	(0.616–6.268)	0.254
Atrial fibrillation	1.997	(0.650–6.136)	0.227	1.547	(0.486–4.923)	0.460
BNP ($\geq$ 100 pg/mL)	0.760	(0.296–1.954)	0.569	0.818	(0.302–2.213)	0.692
%DL_{CO} ($<70\%$)	3.270	(1.356–7.882)	0.008	3.447	(1.343–8.846)	0.010
Euro score II	1.068	(0.783–1.455)	0.678	1.174	(0.853–1.615)	0.325
STS score	1.050	(0.882–1.249)	0.586	0.968	(0.800–1.172)	0.740
Operative time (min)	1.005	(0.997–1.013)	0.212	1.003	(0.995–1.012)	0.424
Pump *time* (min)	1.002	(0.981–1.024)	0.828	1.003	(0.980–1.026)	0.818
Aorta clamp *time* (min)	1.001	(0.978–1.024)	0.945	1.004	(0.981–1.029)	0.711

Propensity scores were calculated by age, sex, BMI, %VC and hemoglobin, and 70 patients with %$DL_{CO} < 70\%$ and 67 patients with %$DL_{CO} \geq 70\%$ were matched

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *BSA* body surface area, *NYHA* New York Heart Association, *%VC* percent predicted vital capacity, *STS* Society of Thoracic Surgeons, *%DL_{CO}* percent predicted diffusing capacity of lung for carbon monoxide

and decrease the functional residual capacity, which affects pulmonary gas exchange properties by increasing ventilation/perfusion mismatches. Thus, DL_{CO} might also decrease after surgery. Preoperative and postoperative chest physical therapy has significantly reduced the number of patients who develop atelectasis, but it does not significantly benefit patients who develop respiratory complications due to infection [20]. Improving the preoperative respiratory status of these patients via the fine adjustment of medication therapy and strict physiotherapeutic control seems important. Preoperative short-term pulmonary rehabilitation for such patients improves the pulmonary function and reduces the incidence of atelectasis, consolidation, and pneumothorax [16]. Preoperative physical therapy with inspiratory muscle training for at least 2 weeks reduced the incidence of postoperative pulmonary complications by 50% [18]. Although the present study did not uncover evidence as to whether surgical outcomes would improve with preoperative short-term pulmonary rehabilitation, determining the correct timing of surgery is also important for avoiding respiratory decompensation.

The present study is associated with several limitations. Although all data were prospectively recorded, this was a retrospective, single-institute study. The retrospective design is susceptible to various sources of bias, which might have not been identified or controlled. The preoperative PFTs were performed according to requests from clinicians, who were not blinded to the results of the PFT. Thus, the possibility that patient management might have been affected by the PFT results cannot be excluded.

In conclusion, the %DL_{CO} seems to be a powerful predictor of postoperative complications. To the best of our knowledge, this is one of the few studies to assess whether DL_{CO} is a potential risk factor for adverse outcomes of patients after cardiac surgery. Preoperative DL_{CO} values might provide more accurate prognostic information about outcomes after cardiac surgery. Preoperative PFT findings might provide clinicians with more accurate risk profiles as well as additional prognostic information. Thus, pulmonary function testing, including measurement of DL_{CO}, should be a routine component of preoperative evaluations.

Acknowledgements The authors thank Yasuo Haruyama, MD, PhD, Department of Public Health, Dokkyo Medical University, for helping with the statistical analyses.

Funding This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in association with the present study.

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