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

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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. The DL_{CO} was routinely determined in all patients. A reduced DL_{CO} was clinically defined as $\%DL_{CO} <70\%$. The $\%DL_{CO}$ 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 $\geq70\%$ and $<70\%$, respectively. Complications were associated with in-hospital mortality ($P < 0.001$), but not the $\%DL_{CO}$ ($P = 0.275$). 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: The $\%DL_{CO}$ 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.

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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, the DL_{CO} is less influenced by patient effort [2]. The 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].

The DL_{CO} depends on two resistances arranged in series according to the following equation:

$$1/DL_{CO} = 1/D_M + 1/\theta_{CO} V_C \text{ [3-5]}$$

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 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.

The DL_{CO} is an equally powerful predictor of postoperative complications in patients with and without COPD after lung resection. A previous study suggested that the 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, the 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 the 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 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 the 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.

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

We measured the 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, then a carbon monoxide-helium mixture was forcefully inhaled to total lung capacity, and held for 10 seconds and then exhaled. The patients exhaled to wash out the estimated mechanical and anatomical dead space. Alveolar samples were then collected, and the 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 DL_{CO} was determined from regression equations according to age, height, and sex (Predicted DL_{CO} for men, 15.5× Body Surface Area (BSA) - 0.23 × Age + 6.8; Predicted DL_{CO} for women, 15.5 × BSA - 0.117 × Age + 0.5) [7]. The $\%DL_{CO}$ was calculated by dividing the actual DL_{CO} by the predicted 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 hours. 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 to 4, using the operational definitions of postoperative pulmonary complications described by Kroenke et al. (Table 1) [8]. 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 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; Gade3: n = 61, Grade4: n=3). Figures 1 and 2 show the relationship between patients with all complications or respiratory complications and the $\%DL_{CO}$ 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 were 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 the %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 a %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 y; 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. 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, the %VC was significantly different (95.65 ± 16.1% vs. 89.6 ± 16.5%; P = 0.005) whereas the 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).

The %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), 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]. The 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 a %DL_{CO} of <70% than among those with a %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, the %DL_{CO} might be a marker of heart failure. A previous study suggested that cardiac surgery may also contribute to a greater reduction in the DL_{CO}. The mechanism underlying the reduction of the 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 >3-fold 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 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 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 the 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 the DL_{CO}, should be a

routine component of preoperative evaluations.

Compliance with ethical standards

Conflict of interest: The authors declare no conflicts of interest in association with the

present study.

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Figure legends

Fig. 1. Patients with all complications after surgery and the %DL$_{CO}$ quartiles.

The %DL$_{CO}$ quartiles were as follows: Q1 ($\leq$ 74.6%), Q2 (74.7% – 88.8%), Q3 (88.9% – 101.7%), and Q4 ($\geq$ 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 ($\leq$ 74.6%), Q2 (74.7% – 88.8%), Q3 (88.9% – 101.7%), and Q4 ($\geq$ 101.8%). The ORs were adjusted as described in the Figure 1 legend. DL$_{CO}$, diffusing capacity of lung for carbon monoxide; OR, odds ratio. Error bars represent 95% confidence intervals.