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ORIGINAL ARTICLE

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Early exercise pulmonary diffusing capacity of carbon monoxide after anatomical lung resection: a word of caution for fast-track programmes

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Key question

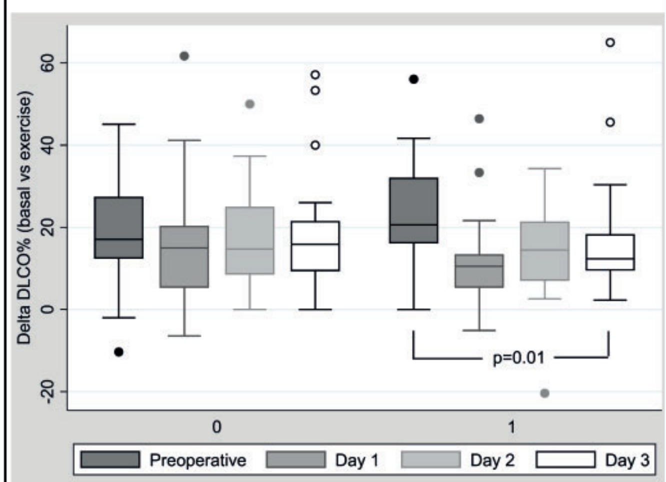
Would the delta percent in the DLCO% (before and after exercise) be affected by the size of the anatomical lung resection?

Key finding(s)

DLCO% is impaired after large resections. The physiological increase in the DLCO% after exercise is far from normal on the 3rd day.

Take-home message

Large resections (4 or more segments) show a DLCO% severely impaired even after exercise, posing unexpected risks with very early discharge.



Abstract

OBJECTIVES: In healthy individuals, increasing pulmonary blood flow during exercise also increases the % of the diffusing capacity of the lungs for carbon monoxide (DLCO%), but its evolution after lung resection is unknown. In this study, our goal was to measure changes in exercise DLCO% during the first 3 days after anatomical lung resection.

METHODS: We performed a prospective observational study on consecutive patients with non-small-cell lung cancer scheduled for anatomical resection, except pneumonectomy, during a 6-month period. Patients underwent measurement of the DLCO% by a single-breath technique adjusted by the concentration of haemoglobin—before and after standardized exercise the day before and

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3 consecutive days after surgery. The delta (Δ) variation (basal versus exercise) was calculated. The number of functioning resected segments was calculated by bronchoscopy. Postoperative pain and pleural air leak were estimated using a visual analogue scale and graduated conventional pleural drainage systems, respectively, and their influence on ΔDLCO each postoperative day was evaluated by linear regression analysis.

RESULTS: Fifty-seven patients were included. The visual analogue scale of pain and pleural air leaks were not correlated to Δ values (model R^2: 0.0048). The evolution of Δ values during 3 postoperative days showed a progressive recovery of values, but on the third day, DLCO% capacity during exercise was still impaired ($P < 0.01$), especially in patients who underwent a resection of more than 3 functioning segments.

CONCLUSIONS: Physiological increase in DLCO% during exercise is still impaired on the third postoperative day in patients undergoing resection of more than 3 functioning pulmonary segments. This fact should be considered before discharging those patients after anatomical lung resection.

Keywords: Pulmonary diffusing capacity for carbon monoxide • Lung resection • Perioperative care • Postoperative recovery

INTRODUCTION

Diffusing capacity of the lung for carbon monoxide (DLCO) is currently considered one of the most important risk factors for postoperative complications after lung cancer surgery [1]. For that reason, it is mandatory to measure it during the preoperative workout of any patient in need of an anatomical lung resection [1]. Another interesting characteristic of the DLCO in healthy subjects is its capacity to increase with exercise in response to the increase in pulmonary blood flow. This increase in the DLCO is measurable, and its impairment during the preoperative workout has been correlated with the occurrence of postoperative complications after lung resection [2]. Despite the importance of this factor, little is known about the evolution of the DLCO during the immediate postoperative period.

In recent years, fast-track programmes for patients having lung cancer surgery have been implemented in clinical practice to reduce costs [3] without compromising postoperative outcomes [4]. We hypothesized that after anatomical lung resection, the respiratory physiological response to exercise can be impaired, posing an unexpected risk for the patient if he or she is discharged too early. Accordingly, the aim of this study was to analyse the evolution of the physiological increase in DLCO after a standardized exercise protocol during the first 3 postoperative days and comparing those values to the preoperative data.

MATERIALS AND METHODS

Studied population

This prospective observational study was performed with consecutive patients who had non-small-cell lung cancer (NSCLC) who were scheduled for anatomical lung resection. Patients were recruited between September 2017 and February 2018. Inclusion and exclusion criteria were the same during the recruitment period. Patients were selected for lung resection according to the evidence-based recommendations of the American College of Chest Physicians [1]: in short, a Karnofsky performance status greater than 50%, no other comorbidities having a worse prognosis than lung cancer, predicted postoperative forced expiratory volume in 1 s (ppoFEV1) >30% and/or predicted postoperative DLCO (ppoDLCO) >30% or VO_2 max (maximal aerobic capacity) >10 ml. No age limit was imposed. Patients were excluded from the study if an extended resection to the chest wall or diaphragm was foreseen, if they received preoperative induction chemotherapy or if they were unable to complete the preoperative incremental standardized exercise protocol (see below). After surgery, the absence of a large postoperative air leak—scoring 4 or 5 on the graduated conventional pleural drainage system—was also considered a must to perform the exercise routines required for the study (see below). If a large air leak occurred, the patient was operated on to control the leak, and she/he would be excluded from the study.

Perioperative management

All patients were operated on by or under the direct supervision of senior thoracic surgeons using minimally invasive approaches [muscle-sparing axillary minithoracotomy or the 3-port video-assisted thoracic approach (VATS)], depending on the characteristics of the tumour. Only patients considered fit for surgery were offered the opportunity to enter the study. Once they agreed, the patients signed informed consent forms, with the proviso that they could stop participation at any point. The study was approved by the local institutional review board (PI 10310/2017).

Preoperative management was standardized. Patients were encouraged during the outpatient consultation to quit smoking, if needed, and were instructed to start physical conditioning (walking, coughing manoeuvers and incentive spirometry). Pharmacological therapy was reviewed and updated when indicated. Anaesthesia procedures were performed by specialized senior anaesthetists. All patients were extubated in the operating room, transferred to the recovery room for the next 6 h and then moved to the thoracic surgery ward when no complication was detected. Chest physiotherapy was started in the recovery room; after transfer to the ward, patients were helped to start walking as much as possible [5]. One chest tube was left in place and was connected to a conventional chest drain—provided with an analogue scale (1–5) to measure potential air leakage—under no suction.

Postoperative analgesia and pain evaluation

Pain control was achieved by means of bupivacaine infusion through an epidural catheter in axillary thoracotomy cases or by paravertebral blocks in VATS cases and supplemented with non-steroidal anti-inflammatory drugs: acetaminophen 1 g/8 h intravenously or orally depending on intake plus ibuprofen 600 mg/8 h orally. Pain intensity was recorded by means of a 10-point visual analogue scale (VAS) after the standard morning dose of analgesia and before inviting the patient to proceed with the daily routine. Analgesia was titrated, the goal being to keep pain between 1 and 2 and always under 4 for a comfortable test.

Air leak assessment

Immediately before DLCO measurements were performed, air leakage was evaluated after 5 consecutive forced expiratory manoeuvers. Patients with air leaks scoring 4 or 5 on the analogue scale were considered non-eligible, and the study was not performed on that day.

Study routine

Diffusing capacity of the lung for carbon monoxide measurement. HypAir equipment from Medisoft (Medisoft Belgium, Sorinnes, Belgium) was used for DLCO measurements using the helium single-breath method [6]. The equipment was calibrated and adjusted for temperature and humidity every day before any procedure. Measurements were recorded during the study if, at the end of the procedure, the quality of the manoeuver was evaluated as good (marked in green) by the system. Each patient repeated up to 3 manoeuvers, with 5 min of rest between each one. The best data were finally recorded. Daily quantification of the patient's haemoglobin level was performed before initiating the study measurements.

Measurements were performed when the patient was admitted and on the first, second and third postoperative days before and after the exercise protocol. The ΔDLCO was calculated for each pair of values according to the formula:

$$\Delta DLCO = ((DLCO\ after\ exercise - basal\ DLCO\ before\ exercise)/DLCO\ before\ exercise) \times 100$$

Exercise protocol. The exercise protocol was performed on a Lode Corival™ bicycle ergometer (Lode B. V., Groningen, Netherlands) in the ward's physiotherapy facilities under constant monitoring of peripheral O_2 saturation and a complete electrocardiogram. A high-intensity intervallic protocol was used. This protocol was initiated with a warm-up period of 3 min of constant pedalling without resistance followed by a maximum of 15 min of exercise in which the patient was asked to pedal at a rate of 60 revolutions/min. In this second phase, the patient pedalled against a resistance (minimum 35 W) for 2 min followed by 3 min of pedalling without resistance until limiting symptoms appeared or until exhaustion or the end of the protocol. The maximum exercise reached was registered in watts and converted into percentage of the theoretical value for the patient's gender, age and height [7]. Reasons for premature ending or cancelling the daily routine were also recorded.

Complications and the 30-day mortality rate of the series were registered. All studied variables and outcomes were defined and recorded prospectively on a customized computerized database.

Data analysis

After the Shapiro–Wilks normality test for continuous variables, the patients' characteristics (age, sex, body mass index and comorbidity), preoperative data (FEV1%, ppoFEV1%, DLCO%, ppoDLCO% and exercise capacity in watts) and intraoperative (type of approach and resection and number of functional resected segments) and postoperative data were presented as frequency tables, mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate. The influence of pain and postoperative air leak on the measured DLCO% was studied by linear regression analysis, where ΔDLCO% was the dependent variable, and the VAS value and air leak score were the independent variables. Preoperative DLCO% and ΔDLCO% values

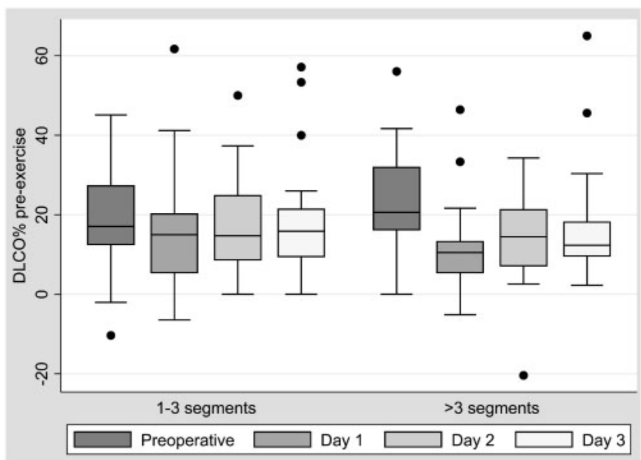

Figure 1: Box plot of pre-exercise variations in DLCO% after exercise by the number of removed non-obstructed pulmonary segments. Preoperative and postoperative days 1–3 are shown. DLCO%: the % of the diffusing capacity of the lungs for carbon monoxide.

Table 1: Respiratory function values of the 57 patients in the series

	General series		Three or fewer segments resected	Four or more s egments resected
	Mean[a] ± SD	95% CI	Mean[a] ± SD	Mean[a] ± SD
FVC	92.8 ± 2.2	88.5–97.2	90[b]/24[b]	94.9 ± 14.4
FEV1	88.7 ± 2.3	84.1–93.4	86.4 ± 17.6	92.4 ± 16.7
FEV1/FVC	100[b]/12[b]		98[b]/15[b]	102[b]/10[b]
DLCO%	82.1 ± 2.7	76.6–87.6	81.4 ± 20.7	83.1 ± 20.9
ppoDLCO%[c]	67.3 ± 2.3	62.7–72	70.2 ± 18	62.7 ± 16.1

[a]Values are presented as mean and SD after normality analysis.

[b]Values presented as median and interquartile range.

[c]Predicted postoperative values calculated according to the number of functional pulmonary segments resected without obstruction at bronchoscopy.

CI: confidence interval; DLCO%: the % of the diffusing capacity of the lungs for carbon monoxide; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; ppo: predicted postoperative; SD: standard deviation.

Table 2: Percent of the diffusing capacity of the lungs for carbon monoxide before and after the exercise protocol from the day of admission to the third postoperative day

	Admission	First day	Second day	Third day
Number of patients	57	57	57	57
Pre-exercise				
Mean ± SD	82.1 ± 2.7	56 ± 1.8	59.5 ± 1.9	60.1 ± 2.1
95% CI	76.6–87.5	52.5–59.6	55.6–63.3	56–64.2
Post-exercise				
Mean ± SD	98.5 ± 3.2	64 ± 2.2	68.3 ± 2.2	70.2 ± 2.6
95% CI	92–105	59.6–68.5	64–72.7	65–75.3

CI: confidence interval; SD: standard deviation.

Table 3: Influence of air leak and pain on post-exercise % of the diffusing capacity of the lungs for carbon monoxide (postoperative days 1–3)

Variables	Coefficient	95% CI	*P*-value	R^2	*P*-value
Day 1					
Pain (VAS)	-0.4	-2.7 to 1.9	0.7	0.003	0.91
Air leak	-0.3	-7.7 to 7.1	0.9		
Constant	65.7	56.4–74.9	0.000		
Day 2					
Pain (VAS)	-1.26	-3.2 to 0.67	0.2	0.06	0.17
Air leak	-3.3	-10.4 to 3.8	0.35		
Constant	73.5	66.3 to 80.7	0.000		
Day 3					
Pain (VAS)	-2.1	-4.7 to 0.46	0.1	0.09	0.07
Air leak	-5	-14.9 to 4.9	0.3		
Constant	77.3	69–85.5	0.000		

CI: confidence interval; VAS: visual analogue scale.

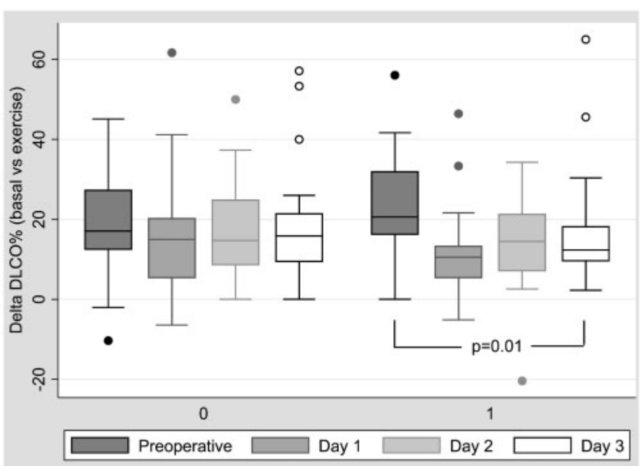

Figure 2: Box plot of the delta values of basal and post-exercise DLCO% measured at hospital admission and on postoperative days 1 to 3, according to the number of functional pulmonary segments removed. DLCO%: the % of the diffusing capacity of the lungs for carbon monoxide.

were compared to daily postoperative values using the paired *t*-test or Wilcoxon matched-pairs rank test as appropriate, depending on the distribution of the variables.

RESULTS

Seventy-six patients were initially included in the study. Complete postoperative 3-day records were available in 57 cases (47 men). Failure to complete the study was due to early hospital discharge on the second postoperative day (5 cases); to non-anatomical resection after a frozen section of the lesion was found to be benign (2 cases); to transitory equipment malfunction (1 case); and postoperative events (11 cases): symptomatic atrial fibrillation (3 cases), chest pain (2 cases), orthostatic hypotension (2 cases) and inability to maintain the necessary apnoea for measuring DLCO (4 cases).

The mean age was 65.5 years (SD: 1.3) and the mean body mass index was 27.2 (SD: 0.5). Functional respiratory characteristics are summarized in Table 1. With the preoperative incremental exercise test, patients completed a median of 123.5 w (IQR: 49.5), corresponding to 97.5% (IQR: 26.7) of their theoretical exercise capacity for gender, age and weight [6]. Fifty-five patients were operated on using VATS, with no conversions, and 2, with a muscle-sparing axillary thoracotomy.

Anatomical lung resection was performed in all patients. The number of segments removed was 1 in 1 patient (1.75%), 2 in 6 patients (10.5%), 3 in 22 cases (38.6%), 4 in 10 cases (17.5%), 5 in 16 cases (28.1%) and 7 in 2 cases (3.5%). The number of functional (free of obstruction at bronchoscopy) segments resected was 3 or less in 35 cases (61.4%) and 4 or more in 22 cases. There were no deaths in the series. Postoperative adverse events were recorded in 11 patients (19.3%): prolonged air leak (more than 5 days) in 5 cases, all scoring 1 or 2 out of 5 on the graduated conventional drainage device; nosocomial pneumonia (diagnosed on postoperative days 4 and 5, respectively) in 2; and atrial fibrillation, hypertensive crisis, pleural empyema and chylothorax in 1 case each. Cardiovascular complications were easily treated with medication, and patients were able to complete the study routine without additional problems.

Mean preoperative and postoperative basal and post-exercise DLCO% values are shown in Table 2. Figure 1 shows the changes in the pre-exercise DLCO%, grouped by the number of functional pulmonary segments removed at surgery from admission to the third postoperative day. All postoperative values were different from the basal values ($P < 0.0001$ in all cases). VAS analysis showed that patients scored their pain a mean of 3.6 ± 2 on day 1; a median of 3 and an IQR of 4 on postoperative day 2, and a mean of 2.7 ± 2.1 on postoperative day 3. Post-exercise DLCO% values were independent of pain measured on the VAS and of air leak (Table 3).

Preoperative and postoperative ΔDLCO% values, according to the number of functional segments removed, are shown in Table 4 and depicted in Fig. 2. The increase in the DLCO%, measured as delta values, was not statistically different in patients with fewer resections (1–3 segments). However, values were lower each postoperative day in cases with 4 or more functional segments removed ($P < 0.05$ in all measurements).

DISCUSSION

Rationale of the study

Perioperative management in patients who had a lung resection has been standardized in many centres to decrease costs of care without compromising outcomes. This management policy is not

Table 4: Delta values of basal and postexercise DLCO% measured at hospital admission and on postoperative days 1–3, according to the number of functional pulmonary segments removed

	1–3 segments removed	P-value[a]	Four or more segments removed	P-value[a]
ΔDLCO%				
Preoperative, mean (SD)[b]	18.4 (11.6)		23.7 (12.4)	
Postoperative day 1, median (IQR)	15 (15.1)	0.0948	10.5 (9.7)	0.0055
Postoperative day 2, mean (SD)	16.4 (11.3)	0.4662	14.5 (11.6)	0.0036
Postoperative day 3, median (IQR)	15.9 (12.3)	0.4414	12.3 (9.6)	0.0142

[a]Comparing postoperative days 1–3 to preoperative values.

ΔDLCO%: change in the % of the diffusing capacity of the lungs for carbon monoxide; IQR: interquartile range; SD: standard deviation.

new in thoracic surgery, and successful experiences of early patient recovery pathways published more than 20 years ago can be found in the literature [8], including a series of patients undergoing lung lobectomy as an outpatient procedure [9]. The widespread use of minimally invasive thoracic approaches has facilitated the implementation of fast-track programmes due to the lower probability of postoperative pain and adverse events in those cases [10]. Although sound scientific evidence is still lacking on the effectiveness of fast-track standardized care for lung resection [11], many teams are concerned about early patient discharge programmes.

In previous publications, we demonstrated that pulmonary function after lobectomy is still severely impaired at the time the patient is discharged from the hospital [12] and that actual FEV1% during hospitalization, and not ppoFEV1% [13], correlates with the occurrence of postoperative cardiopulmonary adverse events. This fact justifies the need for nursing care for patients after hospital discharge to ensure that they keep themselves physically active as much as possible to avoid delayed pulmonary morbidity. Even though preoperative DLCO% and ppoDLCO% are some of the main correlates of postoperative cardiopulmonary complications [1], we failed to find any papers reporting the situation of pulmonary DLCO% in the early postoperative period when the patient is still hospitalized. According to a previous report [14], in patients having a lobectomy, DLCO% is around 13% lower than ppoDLCO% at the time the patient is discharged, but there is no information on DLCO% values during the early postoperative days, when most complications originate.

Measuring early postoperative DLCO% after exercise would be even more interesting, as was shown by Wang *et al.* [2]. They found that patients who developed complications after lung resection had only a limited increase in DLCO% during exercise, measured before surgery. Thus, we have hypothesized that an increase in DLCO% after exercise is impaired in the early postoperative period and that it is still low at the expected discharge time for fast-track programmes (around the third postoperative day), representing a potential factor for decreased exercise capacity and development of delayed surgical complications. In a previous report, we tested the feasibility of measuring DLCO% before and after exercise in the early postoperative period after anatomical lung resection [15].

Physiology of diffusing capacity of the lungs for carbon monoxide during exercise

Although ageing is associated with a reduction in alveolar capillary surface area due to deterioration in the structure and function of the pulmonary circulation [16], broadening of the pulmonary capillary network does not become restricted during exercise in healthy elderly individuals regardless of age [17]. Increasing cardiac output is the most important determinant of increasing DLCO [18]. Besides increased cardiac output and an enlarged pulmonary capillary network, other sources are responsible for raised DLCO during exercise, as described by Hsia [19]: lung expansion, increased pulmonary haematocrit and homogeneous distribution of erythrocytes among capillaries. Even after pneumonectomy, the remaining lung can increase capillary recruitment up to 50% [20] to preserve a patient's exercise capacity.

In patients with mild to moderate chronic obstructive pulmonary disease, as some of the patients with lung cancer are, exercise reveals abnormal physiological responses such as increased pulmonary artery pressure and reduced pulmonary artery compliance [21]. Little is known about the effect of exercise in the immediate period after lung resection. Six months after lobectomy [22], pulmonary arterial pressure is significantly increased during exercise without any changes in cardiac index or in the capillary wedge pressure, and it could be hypothesized that these changes are also present in the early days after the operation, but scant data can be found in the literature regarding haemodynamic and functional changes in the early postoperative period.

Main findings of this investigation and prospects

The main finding of this study was that after resection of 4 or more functional pulmonary segments, the physiological increase of the DLCO% after exercise was impaired at least up to the third postoperative day. In contrast, if the resection was limited to 1–3 functional segments, the DLCO% increase in exercise was comparable to that recorded before the operation. In a large retrospective study by Pezzi *et al.* [23] on patients with NSCLC undergoing lung resection, the authors reported a 90-day mortality rate that was almost double that after 30 days. Those authors did not describe the causes of delayed postoperative death. We found that delayed cardiopulmonary complications were the main cause of death 6 months after pneumonectomy [24]. It could be hypothesized that after a large pulmonary resection, some patients are not able to increase pulmonary blood flow and, consequently, DLCO, despite the absence of clinically detectable cardiac or pulmonary dysfunction. Such a functional limitation could be responsible for decreased physical activity ending in delayed cardiopulmonary complications. This new hypothesis should be tested prospectively, and if confirmed, postoperative protocols designed to increase patients' physical activity after discharge should be implemented. The cost of those programmes should be balanced against the economic benefits of shortening hospitalization periods [25, 26].

Control of bias and limitations of the study

The main limitation of this study is the number of drop-offs in the series, limiting its applicability in other settings. As mentioned previously, in 25% of the cases, we failed to complete all requested postoperative measurements. Although in several cases the reason was early patient discharge, which resulted in missing DLCO values for the third postoperative day, some minor treatable complications—mainly transient atrial fibrillation and hypotension—led us to cancel some of the studies or finish them prematurely. Three of the 5 patients in whom the DLCO could not be measured on the third day because those patients were discharged early were in the group with the low numbers of resected segments. Two patients had orthostatic hypotension on postoperative day 1 that was related to the placement of the epidural catheter that was used because of a muscle-sparing thoracotomy performed to remove a large tumour. In 2 of the 3 patients who had postoperative atrial fibrillation, it occurred on postoperative day 2. Less than 24 h were needed to reverse to sinus rhythm; the patients were able to complete the routine on day 3. The third patient had atrial fibrillation on day 3. It was also controlled within hours and the patient was discharge on day 4. Although the pain was well controlled for most patients, 2 needed extra measures for pain control on day 1, which prevented them from performing the routine. VATS was used for both patients. Neither of these patients with incomplete measurements were among those who had postoperative pneumonia, empyema or chylothorax. They had standard complications that precluded completion of the study routine but did not change the day of discharge or limit the value of the results. In another 4 patients, DLCO values were not obtained due to the patients' incapacity for the necessary apnoea. Wang *et al.* [2] solved this problem by using 3 separate equations (the 3EQ-DLCO method) to describe carbon monoxide uptake during each phase of the breathing manoeuver: inhalation, breath holding and exhalation. This procedure makes the measurement of DLCO independent of the 10-s period of breath holding. With the use of the 3EQ-DLCO technique, we could have recruited 4 additional cases, but this limitation did not affect the results in the remaining cases.

Postoperative basal DLCO% was decreased, as expected. Some variables may account for that, with postoperative pulmonary interstitial oedema on the operated side and chest pain being the main limiting factors. Pain was adequately controlled in the study, and we did not find that it had any influence. DLCO was not attempted until the patient reported no or minimal pain. Pulmonary oedema rarely happens after lung resection less extensive than pneumonectomy [27], but several intraoperative and postoperative variables can contribute to transient increases in capillary permeability: extensive lymph node dissection [28], increased capillary pressure due to acute reduction in the vascular bed and excessive fluid upload [29]. The influence of subclinical interstitial oedema could not be controlled in this study; perioperative management was comparable in all cases, and no patient included in this series showed symptoms of cardiac insufficiency or pulmonary hypertension.

The results we have shown here are probably not applicable to patients receiving induction chemotherapy. Several authors [30] have found up to a 21% decrease in DLCO following induction chemotherapy and radiochemotherapy. This subset of patients deserves further analysis.

CONCLUSIONS

We can conclude that in the immediate period after lung resection, DLCO% is severely impaired. Although patients who had small anatomical resections (3 or fewer segments) can recruit the pulmonary capillary network during exercise to increase DLCO, in cases in which 4 or more functional pulmonary segments are removed, the physiological increase of DLCO during exercise is compromised at the expected hospital discharge time. This finding could be one of the variables influencing delayed cardiorespiratory complications and the patient's readmission.

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Conflicts of interest: none declared.

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