ROLE OF EXERCISE DIFFUSING CAPACITY IN THE PREOPERATIVE EVALUATION OF PATIENTS FOR LUNG RESECTION

by

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ABSTRACT

Introduction: Pulmonary diffusing capacity for carbon monoxide (DLCO) at rest has been shown to be useful in the preoperative evaluation of patients for lung resection. DLCO increases during exercise but may not increase adequately if the pulmonary vascular bed is reduced by emphysema.

Objective: The purpose of this prospective study is to evaluate whether lack of an adequate increase in DLCO during exercise is associated with increased postoperative complications following lung resection.

Methods: We used a modification of the single breath DLCO technique, the 3-equation method (3EQ-DLCO), to determine DLCO during exercise in 57 patients undergoing lung resection at Vancouver General Hospital since October 1998. 3EQ-DLCO was determined during steady state exercise at 35% and 70% of the maximal workload reached in a progressive exercise test. Postoperative complications occurring within 30 days after resection were classified into mortality, cardiovascular and pulmonary complications. Maximal oxygen uptake, DLCO at rest, and the increase in DLCO during exercise, were compared in relation to postoperative complications.

Results: Complications occurred in 19 patients (33%) and included mortality in 2 (4%), cardiovascular morbidity in 12 (21%), and pulmonary morbidity in 13 (23%). Pneumonia in 12% and atrial fibrillation in 18% of patients, were the major pulmonary and cardiovascular

complications. Patients with complications had lower resting DLCO (RDLCO), lower increase in DLCO from rest to 70% of maximal workload expressed as % of predicted DLCO at rest ((70%-R)DLCO%), and lower maximal oxygen uptake, than patients without complications. Results suggested (70%-R)DLCO% was the best preoperative predictor of postoperative complications; a cut-off limit of 10% was the best index to identify complications, with a complication rate of 100% in patients with (70%-R)DLCO% < 10%, compared with a complication rate of 10% in patients with (70%-R)DLCO% ≥ 10% (sensitivity = 78%, specificity = 100%).

Conclusions: Patients who do not increase their DLCO sufficiently during exercise ((70%-R)DLCO% < 10%) have higher complication rates following lung resection.

The strong correlation between exercise diffusing capacity and postoperative complications is likely due to the contribution of a reduced pulmonary capillary bed to cardiopulmonary complications. Exercise DLCO appear to be useful as an additional test to improve the prediction of postoperative morbidity following lung resection.

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CHAPTER ONE: INTRODUCTION

Lung cancer is the most common cancer in men, and has become the most common cancer in women. The prognosis in untreated cases is poor, and at present the curative treatment for non-small cell lung cancer without metastasis is lung resection. The removal of lung parenchyma from patients, who are usually smokers and may have chronic obstructive pulmonary disease (COPD)[Lange et al, 1990] and compromised cardiovascular or pulmonary status, may lead to cardiopulmonary complications or death. The functional loss resulting from lung resection varies with the extent of resection, the relative function of the tissue removed compared with that of the remaining lung, and the degree of functional impairment prior to surgery. Currently about 30% of patients undergoing lung resection develop cardiopulmonary complications with a 30-day mortality varying between 0.6 and 5% [Kadri and Dussek, 1991; Miller, 1993; Damhuis and Schutte, 1996], depending on the extent of lung resection. Recent mortality rates in two recent studies were similar, 6.8% following pneumonectomy and 3.9% following lobectomy in one study [Kadri and Dussek, 1991], and 5.7% after pneumonectomy, 4.4% after bilobectomy, and 1.4% after lesser resection in another study [Damhuis and Scutte, 1996]

Pulmonary function testing including spirometry, lung volumes, diffusing capacity, oximetry, and arterial blood gases has been used to assess the postoperative risk of lung resection. In selected cases, additional evaluation may include radionuclide lung scanning,

exercise testing, invasive pulmonary hemodynamic measurements, and risk stratification analysis.

The diffusing capacity of the lung for carbon monoxide (DLCO) recently has been shown to be an independent predictor of postoperative outcome. DLCO was an important predictor of mortality and postoperative complications [Ferguson et al, 1988; Markos et al, 1989; Pierce et al, 1994; Ferguson et al, 1995]. Patients with low DLCO had an increased respiratory complication rate after major pulmonary resection [Bousamra et al, 1996]. In our retrospective review of 151 pneumonectomy cases done at Vancouver General Hospital from 1992 to 1997, patients with DLCO $\geq$ 70% predicted had a much lower postpneumonectomy complication rate (27 versus 94%) than patients with DLCO < 70% predicted [Wang et al, 1999]. Exercise testing stresses the entire cardiopulmonary and oxygen delivery systems and assesses the reserve that can be expected and may be needed after surgery [Olsen et al, 1989], and therefore may be useful in the preoperative evaluation of patients with lung cancer [Larsen et al, 1997].

Since diffusing capacity at rest has been shown to be a good predictor of postoperative complications following lung resection, and since exercise testing has been also useful in preoperative evaluation prior to lung resection, we reasoned that evaluation of the effect of exercise on DLCO would be helpful to evaluate the ability of the pulmonary capillary bed to expand and increase its capacity to transfer gas during exercise. Lack of an adequate increase in DLCO during exercise would imply inability of the pulmonary capillary bed to increase with increasing cardiac output during exercise, and would suggest increased likelihood of impairment

in gas exchange following lung resection. The evaluation of the effect of exercise on DLCO has not been previously used in the preoperative evaluation of patients scheduled for lung resection. We therefore undertook this study to evaluate the effect of exercise on DLCO using a modified single breath technique, the three-equation method (3EQ-DLCO) of Graham and Cotton [Graham et al, 1981], which does not require breath holding and therefore can be used easily during exercise.

PREOPERATIVE EVALUATION OF PATIENTS FOR LUNG RESECTION

Since the first well-performed study of pulmonary function testing in candidates for lung surgery was published in 1955 [Gaensler et al, 1955], many attempts have been made to establish criteria to predict postoperative mortality and cardiopulmonary complications after lung resection. The criteria used to select patients for major pulmonary resections are based on clinical data, spirometry, more detailed pulmonary functional assessment, and cardiac evaluation.

Severe abnormalities detected by spirometry indicate an increased risk of pulmonary resection and should prompt further preoperative evaluation and a critical assessment of the patient's overall condition [Zibrak et al., 1990]. Patients with hypoxemia or hypercapnia are at increased risk for morbidity or mortality after thoracotomy [Drings, 1989]. Lung volume determinations may be helpful, and an increase in the ratio of residual volume (RV) to total lung capacity (TLC) is associated with a high incidence of postoperative pulmonary complications [Mittman, 1961]. Previously used tests to evaluate differential function of each lung, such as

bronchospirometry [Neuhaus and Cherniack, 1968] and the lateral position test [Bergan, 1960], have been replaced by radionuclide lung scanning with quantitative measurement of the contribution of each lung to pulmonary ventilation and blood flow [Marshall and Olsen, 1993]. The attractive features of radionuclide lung scanning include its ready availability in general hospitals, negligible risk to the patients, and a fairly high degree of accuracy in the prediction of postoperative pulmonary function [Marshall and Olsen, 1993]. Pulmonary hemodynamic measurements may be useful in selected patients; a right ventricular ejection fraction greater than or equal to 35%, a pulmonary vascular resistance less than 200 dyne*sec*cm^{-5}, and a ratio (pulmonary vascular resistance/right ventricular ejection fraction) less than 5.0 should be associated with low morbidity and mortality after lung resection [Lewis et al, 1994]. A resting saturation of less than 90%, or desaturation greater than or equal to 4% during exercise are significantly predictive of increased mortality and morbidity [Ninan et al., 1997]. Risk stratification analysis, using a multifactorial cardiopulmonary risk index based on conventional cardiac and pulmonary clinical data, was highly predictive of postoperative cardiopulmonary complications [Epstein et al, 1993].

Normal or close to normal preoperative spirometric and DLCO data indicate that the patient's lung function allows for surgery without further testing [Gilbreth and Weisman, 1994]. Patients with preoperative forced expiratory volume in one second (FEV1) < 60% predicted or with DLCO < 60% predicted, who are likely to require lung resection, should be considered for radionuclide lung scanning to estimate postoperative spirometry and diffusing capacity. Results showing predicted postoperative FEV1 and predicted postoperative DLCO greater than 40%

predicted suggest an acceptable surgical risk, and the patient should be referred accordingly. Patients whose predicted postoperative results are less than 40% predicted, will require exercise testing to assess maximal exercise capacity, maximal oxygen uptake, and oxygen saturation [Gilbreth and Weisman, 1994]. Patients with a predicted postoperative FEV1 or predicted postoperative DLCO greater than 35% of predicted values and whose peak exercise oxygen uptake is greater than 15 ml/kg/min could be offered surgery, with the goal of removing the smallest volume of tissue that would be compatible with a cure.

DLCO

The main function of the respiratory system is gas exchange, the elimination of CO2 and the uptake of O2, between the lung and the atmospheric air. Exchange of O2 and CO2 across the alveolus, between alveolar gas and pulmonary capillary blood, occurs by the process of diffusion. Diffusion of a gas occurs when there is a net movement of molecules from an area with a higher partial pressure of that gas to an area with a lower partial pressure. Diffusion of gas into a liquid phase is defined by the Fick Law for diffusion [Forster, 1964]:

$$V = (A*D*(P1-P2))/T \qquad [1]$$

where V is the volume of gas diffusing through the liquid per unit time, A is the surface area of the liquid available for gas exchange, D is the diffusivity of the gas in the liquid which depends on the diffusion coefficient and solubility of the gas in the liquid, P1-P2 is the partial pressure difference of the gas across the liquid, and T is the thickness of the liquid interface through which the gas is diffusing. The alveolar capillary membrane has a 70 m^2 surface area with a

thickness of only about 0.5 μm and is superbly adapted for allowing the uptake of O2 and the elimination of CO2. Despite being a larger molecule, CO2 diffuses 20 times more rapidly than O2 because its solubility in water is 24 times greater. The overall capacity of the lung to transfer gas from the alveolar gas to the pulmonary capillary blood is called the lung diffusing capacity (DL), which is equal to the amount of gas volume transferred in ml per minute divided by the mean alveolar to capillary driving pressure in mmHg. This is just a rearrangement of the Fick Law for diffusion [1] given before, where the combination of area multiplied by diffusivity, and divided by thickness indicates DL, yielding equation [2]:

$$V = (A*D*(P1-P2))/T$$

$$(A*D)/T = V/(P1-P2)$$

$$DL = V/(P1-P2) \qquad [2]$$

where P1 is the alveolar partial pressure, and P2 is the capillary partial pressure.

Assessment of DL for O2 by direct measurement of O2 diffusion is difficult, because O2 uptake is limited mainly by perfusion and not primarily by diffusion, and because the pulmonary capillary partial pressure of O2 is continuously increasing as blood flows along the capillary. The driving pressure for O2 uptake is greatest at the start of the capillary where the capillary partial pressure of O2 is at mixed venous levels, and the driving pressure decreases as the blood passes along the pulmonary capillary and takes up O2; normally the capillary partial pressure of O2 approaches equilibrium with alveolar partial pressure of O2 about 1/3 of the length of the capillary from its beginning to its end. DL is measured by using carbon monoxide as a test gas (DLCO), since CO has a diffusivity similar to O2, but binds to hemoglobin with 210 times

greater affinity then O2, resulting in a negligible pulmonary capillary back pressure for CO. Therefore, the CO driving pressure along the entire capillary is equal to alveolar partial pressure of CO. Thus:

$$DLCO = VCO/PACO \quad [3]$$

where VCO is the amount of volume of CO uptake in ml per minute, and PACO is the alveolar partial pressure of CO in mmHg. DLCO is expressed in ml STPD of CO gas uptake per minute per mm Hg of CO driving pressure. In the normal lung, CO diffusion across the alveolar capillary membrane is diffusion limited and not perfusion limited. In disease, DLCO is not exclusively limited by diffusion, and may be affected by uneven distribution of ventilation, uneven ventilation to perfusion, and uneven distribution of alveolar surface and pulmonary capillary blood volume to alveolar volume. Because of these limitations, DLCO has also been termed CO transfer factor. An important consideration, however, is that diffusing capacity is a single value which is determined by the sum of diffusing capacity of millions of gas exchange units. DLCO is the rate of carbon monoxide transfer from inspired alveolar gas to pulmonary capillary blood [Crapo and Forster, 1989], and it indicates the status of the alveolar capillary membrane.

There are two components of the diffusion of CO from alveolar gas to pulmonary capillary blood: diffusion across the alveolar capillary membrane, and the reaction of CO with the hemoglobin in the red blood cells in pulmonary capillaries. The latter component is determined by the volume of blood in the pulmonary capillary, the hemoglobin concentration in the blood, and the chemical reaction rate of CO with hemoglobin. The two components can be

considered as two resistance in series, where overall resistance to diffusion in the lung = resistance to diffusion in the alveolar capillary membrane + resistance to chemical reaction of CO with hemoglobin in the pulmonary capillary blood. Resistance to diffusion is the reciprocal of diffusing capacity and the two components can be related in the following equation [Forster, 1964]:

$$1/DL = 1/DM+1/(\Theta*Vc) \quad [4]$$

where DL is the diffusing capacity of the whole lung, DM is the diffusing capacity of the alveolar capillary membrane, Θ is the reaction rate of CO with hemoglobin, and Vc is the pulmonary capillary blood volume. Morphometric analysis suggest that alveolar capillary membrane conductance is very high, and the major resistance to CO uptake across the lung in normal subjects, appears to be the reaction rate of CO with hemoglobin and pulmonary capillary blood volume [Crapo et al, 1988]. In disease, there may be reductions in both alveolocapillary surface area (DM) and pulmonary capillary blood volume (Vc). However, changes in DLCO related to position changes or exercise are more due to the changes in the volume and distribution of pulmonary capillary blood than to changes in the alveolar capillary membrane.

DLCO is a standard pulmonary function test used routinely in our institution in the preoperative evaluation of patients for lung resection [Morrison et al, 1989 & 1990]. Previous studies have shown a clear relationship between a low diffusing capacity and poor postoperative outcome after lung resection [Ferguson et al, 1988; Markos et al, 1989; Pierce et al, 1994; Ferguson et al, 1995; Wang et al, 1999]. A low DLCO identifies patients with significant emphysema, and reduced pulmonary capillary vascular bed. The mechanisms that would

predispose emphysematous lung to develop pulmonary edema, include barotrauma from lung ventilation [Dreyfuss et al, 1988; Carlton et al, 1990], hyperperfusion of a diminished pulmonary microvascular bed leading to endothelial damage from increased shear [Fry, 1968; Ohkuda et al, 1978], sequestration of activated neutrophils and platelets [Patterson et al, 1989; Markos et al, 1990; Molad et al, 1993], and postoperative pulmonary hypertension due to the decreased pulmonary vascular bed following lung resection [Reichel, 1972]. Poor right ventricular-pulmonary arterial vascular coupling as a result of resection of part of the pulmonary vascular tree, loss of vascular compliance due to overdistension of the remaining vessels by hyperperfusion, and occlusion of the pulmonary capillary bed by activated neutrophils and platelets, may impair cardiac function [Piene, 1986; Reed et al, 1992; Nishimura et al, 1993] and may lead to arrhythmias [van Wagoner, 1993; Stacy et al, 1992].

Despite the need for accurate estimation of the risk of complications after major lung resection, the use of traditional methods of assessing operative risk provides only a modest ability to predict postoperative morbidity and mortality in patients with significant impairment [Keagy et al, 1985; Kohman et al, 1986]. Newer tests have not met with widespread use because they are expensive and labor-intensive, and few data are available to assess their accuracy. Our retrospective review of 151 pneumonectomy cases confirmed previous studies relating impaired DLCO to increased postoperative complications [Ferguson et al, 1988; Markos et al, 1989; Pierce et al, 1994; Ferguson et al, 1995]. Our previous study showed that the strong correlation between diffusing capacity and postoperative complications after pneumonectomy was due to increased cardiopulmonary complications in patients with impaired DLCO; the cardiopulmonary

complications occurred in 94% of patients with DLCO < 70% predicted as compared with 27% of patients with DLCO ≥ 70% predicted [Wang et al, 1999]. DLCO indirectly reflects alveolar capillary surface area and pulmonary capillary blood volume, provided DLCO has been corrected for any decrease in hemoglobin content. DLCO can indicate the presence of emphysematous changes in the lung [Gelb et al, 1973; Morrison et al, 1989 & 1990] and damage to pulmonary parenchyma. The use of DLCO in addition to clinical data, spirometry, and lung volume assessment improves the prediction of outcome following lung resection.

MEASUREMENT OF DLCO

DLCO can be measured using three methods: the conventional single breath-holding, the steady state and the rebreathing techniques. DLCO can also be estimated from other methods or morphometric measurements of alveolar capillary surface area and pulmonary capillary blood volume [Weibel, 1970-1971]. The most extensively used maneuver is the conventional single breath method. The single-breath CO diffusing capacity (SB-DLCO) was first developed by Krogh in 1915 [Krogh, 1915]. After expiring to RV, the subject inhaled rapidly and fully from a spirometer containing about 1% CO, then exhaled rapidly to half of vital capacity (VC) at which point the initial alveolar gas sample was collected. The subjects held their breath for about 6 seconds before emptying the remaining air in their lungs. The second alveolar gas sample was taken from the second expiration. The concentrations of CO in the two alveolar gas samples were measured. The Krogh equation was used to calculate SB-DLCO:

$$\text{SB-DLCO} = V_A * (\text{STPD correction}) * (60/t) * (1/P) * \ln[F_ACO_0/F_ACO_t] \quad [5]$$

where DLCO is the pulmonary diffusing capacity for CO (ml of CO*min^{-1}*mmHg^{-1}), V_A is the alveolar breath holding volume at ambient pressure and temperature in ml, STPD correction is to change the volume to standard pressure (760 mmHg) and temperature (0°C) dry, F_ACO_0 is the initial alveolar CO concentration determined from the initial alveolar gas sample, F_ACO_t is the final alveolar CO concentration determined from the second alveolar gas sample, P is the total gas pressure in the alveolus (P = barometric pressure-water vapour pressure), t is the breath holding time in seconds, and 60 is to convert the seconds to minutes.

The Krogh method of measuring DL was reevaluated and refined about 40 years later [Forster et al, 1954; Ogilvie et al, 1957]. Ogilvie et al [Ogilvie et al, 1957]modified the Krogh method with the introduction of helium, an inert gas, into the CO in the air mixture. The presence of an inert gas eliminated the need for two alveolar gas samples because the initial CO alveolar concentration could be calculated from the inspired CO concentration multiplied by the expired to inspired helium dilution ratio. After expiring to RV, the subject rapidly breathed in a sample of test gas with known concentrations of CO (0.3%) and He (10%) to TLC, held the breath for about 10 seconds, and expired rapidly to RV. After the initial expired dead space washout volume was discarded, an alveolar sample was collected. Most of the CO uptake takes place during breath holding at TLC, but some CO is taken up during the inspiratory and expiratory phases of the maneuver, which are not instantaneous. Inspiration takes up about 2 seconds and exhalation measured from the start of exhalation to completion of alveolar sample collection can take up to 4 seconds. To help compensate for the lung volume changes, the breath holding time was measured from the beginning of inspiration to the beginning of the alveolar

sample collection (Figure 1). The SB-DLCO was calculated from the alveolar volume of test gas inhaled, the gas concentrations in the exhaled alveolar and inspired gas samples, the total dry gas pressure in the alveolus, and the time of breath holding, according to equation [5].

To compensate for CO uptake during the inspiration and expiration phases of the SB-DLCO, Jones and Meade [Jones and Meade, 1961] proposed measuring the breath holding time from 0.3 of inspiration time to half of the alveolar sample collection time (Figure 1), and reducing the size of the alveolar sample collection immediately following dead space washout. This method is theoretically more accurate and reproducible than the classic Ogilvie method, because it provides less overestimation of DLCO when airflow obstruction is present [Beck, 1994]. Currently, the Jones and Meade method of determining breath holding time is recommended by the American Thoracic Society (ATS) and is widely used and accepted. The ATS has thoroughly reviewed the single breath method and has made recommendations for a standard technique [ATS, 1987] which has been updated recently [ATS, 1995]. Despite standardization of the 10 second breath holding time, the volumes of the dead space washout and alveolar sample collection, and the use of rapid inhalation and exhalation, errors in SB-DLCO measurement can occur [Graham et al, 1981]. Graham et al have shown that even the Jones and Meade method overestimates SB-DLCO measured from a lung model [Graham et al, 1980]. This error is negligible in normal subjects who have little difficulty in maintaining high flow rates, breath holding, and adequate volumes. However, in obstructed patients, because of the greater time taken during the inspiratory and expiratory phases of the SB-DLCO maneuver, where CO uptake occurs at volumes lower than TLC, the SB-DLCO is usually overestimated [Graham et al,

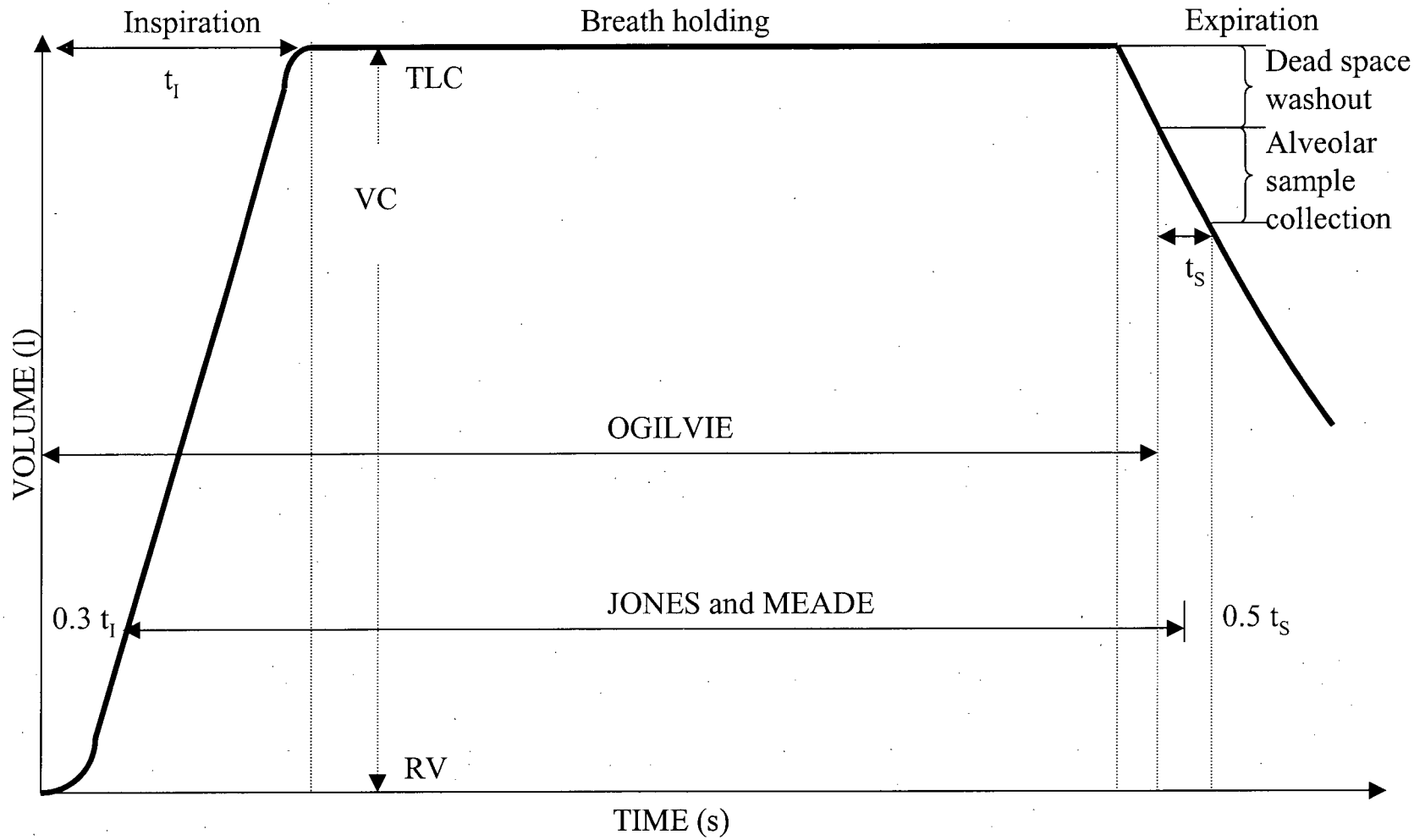

Figure 1. Diagram of SB-DLCO breath-hold timing methods. The original Ogilvie method measures time from the beginning of inspiration to the beginning of alveolar sample collection. The Jones and Meade method measures time from 0.30 of inspiration time to half of the alveolar sample collection time. t_I=inspiration time; t_S=alveolar sample collection time; TLC=total lung capacity; VC=vital capacity; RV=residual volume.

1984].

MEASUREMENT OF 3EQ-DLCO

SB-DLCO may be overestimated by the conventional method because a single equation is used to calculate DLCO, that is valid only for the breath holding phase of the maneuver. In order to avoid problems related to the changing lung volume and timing of the inspiratory and expiratory phases of the SB-DLCO, Graham et al [Graham et al, 1981] used 3 separate equations to describe CO uptake during each phase of the breathing maneuver: inhalation, breath holding, and exhalation (Appendix I). These equations analytically account for the diffusion of CO during the inhalation, breath holding, and exhalation phases of the single breath maneuver, eliminating the need to assume that all CO uptake occurs during breath holding. This makes the measurement of SB-DLCO independent of the maneuver, and increases precision and accuracy of SB-DLCO measurement [Graham et al, 1981], without necessitating a 10 second breath holding maneuver.

In this method, gas concentrations at the mouth and change in lung volume are monitored continuously throughout the single breath maneuver using rapidly responding CO and inert gas analyzers, and a pneumotach. Using the three-equation algorithm, the mean exhaled CO concentration [CO] can be calculated for a predicted DLCO. The calculated [CO] is then compared with the measured [CO], and if not matched, another value of DLCO is used to calculate [CO]. The program then uses a reiterative technique to determine DLCO by matching calculated [CO] and measured [CO] to within 0.1% of each other.

Continuous monitoring of expired gas allows the entire exhaled alveolar gas to be used in the three-equation method instead of using a discrete alveolar sample, which eliminates timing errors, accounts for the CO uptake of the entire lung more accurately, and minimizes the effect of any lung ventilation inhomogeneities. The three-equation method is more accurate and precise than the conventional SB-DLCO method in patients with air flow obstruction, or small lung volumes, or difficulty in breath holding [Graham et al, 1981]; moreover, it is independent of breath-holding time, or inspired or expired flow rates [Graham et al, 1996].

Since breath holding is not necessary, this method is useful in evaluating 3EQ-DLCO during moderate to high intensity exercise where prolonged breath holding becomes difficult. This method was useful in our study because the subjects exercised at moderate intensities and ventilation rates when breath holding became difficult. The 3EQ-DLCO has been used in our laboratory in two previous exercise studies; the first evaluated 3EQ-DLCO during heavy exercise in normal subjects [Potts et al, 1996], and the second evaluated limitation of exercise 3EQ-DLCO in interstitial lung disease as a mechanism leading to exercise hypoxemia [Rai et al, 1998].

EXERCISE CAPACITY

Cardiopulmonary exercise testing has been used extensively in the evaluating patients with lung disease or dyspnea on exertion, in assessing occupational impairment or disability, as

an integral component of pulmonary rehabilitation [Wasserman and Whipp, 1975], and in evaluating ambulatory patients with heart failure being considered for cardiac transplantation [Weisman et al, 1992]. The ability to exercise adequately has also been used to assess the cardiopulmonary risk of lung resection [Olsen, 1989]. Previous work has suggested that an inability to perform minimal exercise or to complete an exercise task is associated with an increased risk for complications after lung resection [Van Nostrand et al, 1968; Reichel, 1972; Miller et al, 1981]. The theoretical value of exercise testing is that it stresses the entire cardiopulmonary and oxygen delivery systems, and assesses its physiological capacity, which could enable one to determine the reserve that can be expected and may be needed after surgery. According to Olsen et al in 1989, the value of exercise testing had not yet been substantiated completely, and the relationship between preoperative exercise function and postoperative outcome needed validation [Olsen et al, 1989].

Stair climbing as a test of endurance has been used for decades by surgeons in evaluation of patients for surgery. van Nostrand et al found that a postoperative mortality rate of 11% in pneumonectomy patients who had been able to climb two flights of stairs while the mortality rate was 50% in those who were unable to accomplish one flight [van Nostrand et al, 1968]. Bolton et al concluded that stair climbing could be used as a reliable screening test of minimal pulmonary function [Bolton et al, 1987]. Olsen et al showed that the ability to climb three flights of stairs preoperatively, statistically separated those patients having a longer postoperative intubation and hospital stay, greater number of complications, and higher cumulative complication score [Olsen et al, 1991]. Pollock et al suggested that stair climbing is more stressful and requires a higher

oxygen consumption (VO2) than cycle ergometry in COPD patients [Pollock et al , 1991]. This technique would be attractive clinically, as it requires no special equipment or expertise.

Exercise limitation following pulmonary resection in many patients could be due to reduced cardiac output. This decrement was believed to be owing to the reduction in the pulmonary capillary bed by surgical resection in combination with other underlying abnormalities in the remaining lung tissue, resulting in elevated pulmonary artery pressures [Degraff et al, 1965]. Reichel reported that no patient who finished a treadmill walking test, conducted in six stages of increasing speed and grade, experienced postoperative complications, while 57% of those who did not complete the test experienced significant postoperative complications [Reichel, 1972]. Berggren et al noted that in patients undergoing lobectomy, postoperative mortality was 7.7% in those who completed more than 83 watts for 6 minutes on a cycle ergometer, but was 22% in those completing less than 83 watts [Berggren et al, 1984]. Fee et al [Fee et al, 1978] determined preoperative arterial blood gas and spirometry at rest, and pulmonary vascular resistance using thermal dilution cardiac output calculation via a flow-directed catheter during treadmill exercise. In all 5 mortality cases, the operative risk was considered to be high when assessed by determination of pulmonary vascular resistance in exercise, while four of five were classified to be at low risk when assessed by arterial blood gases and spirometry at rest. Fee et al concluded that the loss of pulmonary vascular compliance determined postoperative function and survival. Eugene et al suggested that if maximal oxygen consumption (VO2max) was < 1.0 l/min, there was an associated 75% mortality, while if VO2max was > 1.0 l/min, there were no deaths [Eugene et al, 1982]. Smith et al concluded that

determination of VO2max at peak exercise was a very valuable noninvasive method of preoperative evaluation, and in their opinion, superior to the quantitative lung scan prediction of postoperative FEV1 [Smith et al, 1984]. Bechard and Wetstein noted that patients with a maximum VO2 of < 10 ml/kg/min were at significant risk and probably should not be approved for surgery, even if spirometry was acceptable [Bechard and Wetstein, 1987]. Miyoshi et al demonstrated that in-hospital mortality can be predicted by VO2 [Miyoshi et al, 1987]. Nakagawa et al published that fatal complications were best identified on the incremental exercise testing by the calculated oxygen delivery per body surface area at a lactate of 20 mg/dl, which was below 500 ml/min/m^2 in all 4 patients who died and in none of the 27 who survived [Nakagawa et al, 1992]. Corris et al showed that one might be able to predict exercise VO2max postoperatively by using the quantitative lung scan results and the preoperative exercise VO2max [Corris et al, 1987]. It seems logical that evaluation of regional lung function by lung scanning, lung function testing, and maximal exercise oxygen uptake would be complementary in predicting postoperative physiological outcome, as suggested by Markos et al [Markos et al, 1989].

Patients incapable of exercising may be at increased risk because of severe underlying cardiopulmonary disease. Such disease may go unrecognized preoperatively, because exercise and cardiopulmonary stress may be limited by noncardiopulmonary factors, only to become obvious during the stress of the perioperative state. Noncardiopulmonary factors limiting exercise, such as impaired joint motility, muscle weakness or amputation, arthritis or leg pain, claudication, dementia, or the inability to follow instructions, may independently contribute to

increased postoperative risk. Exercise testing measures not only cardiopulmonary fitness, but also nonphysiologic factors, such as determination, perseverance, and willingness to cooperate. An inability to cooperate with postoperative care, or a low threshold for tolerance of discomfort could lead to retained secretions and an increased incidence of postoperative complications. Such patients may develop hypoxemia and increased work of breathing, which might not only lead to pulmonary complications due to retained secretions, but could also precipitate arrhythmias or congestive heart failure.

EXERCISE DLCO

During exercise, the increased metabolic needs of the muscle tissue must be provided for by an increase in oxygen delivery and increased oxygen extraction at the level of the tissue. Despite the decreased transit time of blood in the lung capillary, a low alveolar to arterial PO2 difference is maintained in healthy subjects during exercise. The mechanisms for this adaptation to exercise are an increase in cardiac output, an increase in the effective pulmonary capillary blood volume, and an increase in the diffusing capacity of the alveolar capillary membrane [Johnson et al, 1960]. The increase in alveolar capillary membrane surface area and in pulmonary capillary blood volume results in an increase in diffusing capacity.

Previous studies have evaluated the time course and magnitude of the increase in DLCO during exercise. Billiet found that in 3 young, healthy untrained men exercising just 20 watts lower than the maximum the subjects could tolerate, 85% of the increase in SB-DLCO occurred

within the first 1.5 minutes of steady state exercise [Billet, 1970]. A further 15% increase, amounting to a 2 to 3 $ml*min^{-1}*mmHg^{-1}$ increase in SB-DLCO, occurred within 5 to7 minutes of additional exercise. On cessation of exercise, the SB-DLCO decreased sharply to a value 15% higher than the resting value within minutes, but remained 2 $ml*min^{-1}*mmHg^{-1}$ higher than the resting value 10 minutes after exercise. Potts et al. [Potts et al, 1996] used the three equation method to evaluate 3EQ-DLCO during exercise in normal, healthy subjects. In their study, subjects performed a progressive exercise test on a cycle ergometer to determine maximal workload and VO2max. 3EQ-DLCO was determined in each subject during rest and steady state exercise at workloads of 25%, 50%, 75%, and 90% of the maximal workload. 3EQ-DLCO was noted to increase progressively with increasing workload. At 90% of maximal power output, subjects increased their 3EQ-DLCO by 61% to 75% of the baseline resting DLCO. These observations are consistent with prior studies which have used conventional methods to evaluate SB-DLCO during exercise.

The recent literature and our retrospective review clearly demonstrated that DLCO is an important predictor of postoperative complications [Ferguson et al, 1988; Markos et al, 1989; Ferguson et al, 1995; Wang et al, 1999]. During physical exercise, both the respiratory and cardiovascular systems are under stress because of the increased oxygen requirement of the working muscles and the increased carbon dioxide elimination. An increase in this gas exchange implies a close coupling of pulmonary ventilation and cardiovascular circulation. The response of the cardiovascular and respiratory systems to the increased gas exchange and ventilatory and circulatory requirements in the postoperative period, may be evaluated by preoperative exercise

testing, which would be expected to be useful in the preoperative evaluation of patients with lung cancer. The mechanisms for the increased DLCO during exercise include more homogeneous distribution of red-cell transit time within the capillary network as flow increases [Johnson and Miller, 1968; Presson et al, 1994], dilatation of pulmonary blood vessels, recruitment of previously nonperfused pulmonary vasculature, more homogeneous vertical distribution of pulmonary blood flow [Harf et al, 1978; Lewis et al, 1978; Stokes et al, 1981; Cerrerelli and Di Prampero, 1987; Hasson et al, 1989], greater utilization of existing alveolar and capillary surface as lung volume and pulmonary blood flow increase [Bachofen et al, 1987; Hsia et al, 1992], and increased arterial perfusion pressure [MacIntyre, 1997]. Thus, exercise may serve to identify subjects with subtle diffusing defects who may still have a DLCO in the "normal" range at rest, but show limitation during exercise. The use of exercise DLCO in addition to clinical data, spirometric values, and lung function assessments may result in improved prediction of postoperative outcome following lung resection.

COMPLICATIONS FOLLOWING LUNG RESECTION

Pulmonary resection remains the most effective therapy for lung cancer without metastasis but is associated with a rate of about 30% for cardiopulmonary complications and a 30-day mortality varying between 0.6 to 5% in different reports [Kadri and Dussek, 1991; Miller, 1993; Damhuis and Schutte, 1996]. A decreased oxygen tension in the pulmonary tissue due to diminished cardiopulmonary function could increase the risk of infection or development of tissue necrosis, or could impair healing [Larsen et al, 1997]. Patients with a significantly reduced

DLCO are at higher risk for respiratory insufficiency, particularly in the early postoperative period after major pulmonary resection [Ferguson et al, 1988]. They are also at risk for pulmonary complications as a result of alterations in the alveolar architecture, due to the presence of emphysema [Ferguson et al, 1988]. Successful adaptation to pulmonary resection depends on adequate expansion of the pulmonary vascular bed [Ogilvie, 1963], and patients who fail to adapt in this manner may develop pulmonary hypertension, pulmonary congestion, and pulmonary edema postoperatively. The association of diffusing capacity and cardiac morbidity is not surprising because of the known increase in pulmonary vascular resistance that results from major lung resection [van Miegham and Demedts, 1989; Nishimura et al, 1993]. An increase in pulmonary vascular resistance can cause right heart strain, contributing to the relatively high frequency of cardiovascular complications [Krowka et al, 1987; Patel et al, 1992; Busch et al, 1994]. Cardiac events after thoracotomy usually include atrial arrhythmias and myocardial ischemia; in addition a high incidence (33%) of ventricular arrhythmias has been noted after thoracic operations [Borgeat et al, 1989]. Congestive heart failure and cardiac enlargement can predispose to arrhythmias, and an already enlarged heart would be more prone to develop arrhythmia by this mechanism [von Knorring et al, 1992]. Intraoperative hypotension can significantly increase the risk of both arrhythmia and myocardial ischemia [von Knorring et al, 1992].

Pulmonary edema has been reported to occur in 4 to 15% of patients undergoing pneumonectomy, and is an important factor in over 50% of postoperative deaths [Verheijen-Breemhaar et al, 1988; Patel et al, 1992; Turnage and Lunn, 1993]. In our retrospective study,

pulmonary edema occurred in 13% of 151 pneumonectomy cases and it occurred in 75% of 8 mortality cases [Wang et al, 1999]. Right pneumonectomy, repeat thoracotomy and a more positive fluid balance were identified as risk factors [Verheijen-Breemhaar et al, 1988]. An increase in the edema fluid protein to total serum protein ratio was consistent with increased permeability as a cause of the edema [Mathru et al, 1990]. Cardiac dysrhythmias, especially atrial fibrillation, occur in 10 to 30% of pneumonectomy and lead to an increased mortality of 25% [Krowka et al, 1987; Wahi et al, 1989]. In our retrospective study, cardiac arrhythmias occurred in 21% of 151 pneumonectomy cases and it occurred in 25% of 8 mortality cases [Wang et al, 1999]. Their occurrence has been attributed to hypoxemia, vagal irritation, atrial inflammation from pericarditis, preexisting heart disease, pulmonary hypertension and right heart dilation. Krowka et al also found that dysrhythmias occurred more frequently following intrapericardial dissection and in patients who developed postoperative pulmonary edema [Krowka et al, 1987]. In a lung resection, the patient is usually placed in the lateral decubitus position with the lung to be resected uppermost. This results in increased perfusion of the dependent lung. When the chest is opened, the nondependent lung collapses, compressing its blood vessels. This factor, together with hypoxic vasoconstriction of the operated lung shifts even more of the cardiac output into the dependent lung and worsens ventilation-perfusion mismatching. The anesthetists compensate for this by ventilating the dependent lung with a high tidal volume. When surgeon ligates the pulmonary artery of the lung prior to lung resection, the entire cardiac output then flows through the vascular bed of the dependent lung which is also being ventilated with a high tidal volume. The resulting hyperperfusion of the dependent lung may drastically change the output impedance or afterload seen by the right ventricle. These supraphysiological stresses may lead to pulmonary

edema and cardiac dysrhythmias.

PREOPERATIVE EVALUATION OF PATIENTS FOR LUNG RESECTION USING 3EQ-DLCO

A low preoperative DLCO may identify those patients who have emphysema and a reduced pulmonary capillary bed. They may be prone to postoperative cardiopulmonary complications because of reduction in the pulmonary capillary bed and reduced gas capacity for exchange. The magnitude of DLCO at rest may not be an adequate reflection of true functional capacity of the lung for gas diffusion, because it may not indicate the capacity of DLCO to increase during exercise. The recruitment or increase in DLCO with increasing pulmonary blood flow during exercise is also important in addition to the resting DLCO in evaluating early diffusing capacity abnormalities [Hughes et al, 1991; Hsia et al, 1992]. In exercise, both ventilatory and cardiovascular systems are tested, which can explain the observations that exercise variables are predictive of cardiopulmonary complications and mortality. DLCO increases during exercise but may not increase adequately if the pulmonary vascular bed is reduced by emphysema.

The purpose of this prospective study is to evaluate whether abnormal DLCO is especially useful in predicting postoperative morbidity and mortality following lung resection and whether lack of an adequate increase in DLCO during exercise is associated with increased postoperative complications following lung resection. In this project, we evaluated DLCO during

exercise in subjects with lung cancer prior to lung resection using the 3EQ-DLCO method, and related changes in DLCO during exercise to postoperative complications.

HYPOTHESES

1. Decreased DLCO is associated with increased postoperative mortality and morbidity of patients with lung cancer undergoing lung resection.
2. Lack of an adequate increase in DLCO during exercise is associated with increased postoperative mortality and morbidity of patients with lung cancer undergoing lung resection.
3. DLCO during exercise is better than DLCO at rest in predicting postoperative complications following lung resection.

CHAPTER TWO: METHODOLOGY

ETHICS APPROVAL

Ethical approvals for the study were obtained from the University of British Columbia Clinical Screening Committee for Research and other Studies Involving Human Subjects, and from the Vancouver General Hospital Research Advisory Committee. Copies of the University of British Columbia and Vancouver General Hospital ethics approvals are attached in Appendix II.

SUBJECT RECRUITMENT

All patients with a diagnosis of non-small cell lung cancer undergoing thoracotomy for lung resection at Vancouver General Hospital since October 1998 were evaluated prospectively. We excluded patients who had received radiation treatment or chemotherapy prior to surgery. The diagnosis and staging [Beahrs et al, 1992] were based on one or more of the following: chest radiography and computerized tomogram (CT) scan, sputum cytology, bronchoscopy with bronchial brushing and/or biopsy, or biopsy or cytology of the lung lesion; the final diagnosis was based on the pathology of the resected lung. Mediastinal involvement was generally excluded by mediastinoscopy or CT scan of the chest, and metastasis by CT scan of brain, liver and bone if clinically warranted. Patients were excluded from the study if they were over 85

years old, or had symptomatic ischemic heart disease, severe airflow obstruction (FEV1/FVC < 45%), resting hypoxemia (O2 saturation < 90% at rest), severe restriction (FVC < 1.2 liters), or another disease that could impair exercise tolerance. After getting permission from their treating surgeons at Vancouver General Hospital, subjects who met the selection criteria were informed of the study directly by their treating surgeons, or when they came to the lung function laboratory or preadmission clinic for preoperative evaluation, or when they were admitted to the thoracic surgery ward for evaluation prior to surgery, or by mailing them a recruitment notice (Appendix III) requesting them to volunteer for the study. All subjects read and signed an informed consent form (Appendix IV) prior to participation in the research study.

PATIENT EVALUATION

Clinical evaluation

Each subject's clinical history, lung function and radiological findings were reviewed by myself and my supervisor Dr. Raja T. Abboud (both are respirologists), and the patient was clinically examined prior to being included in the study. In addition to reviewing the thoracic surgeon's chart and consultation letter, we administered a brief clinical questionnaire which documented current clinical symptoms, physical examination, smoking history, medications and allergies, and any other detailed history (Appendix V). Height was measured to the nearest centimeter with the subjects standing upright without shoes. Body weight to the nearest half kilogram was determined with the subjects wearing light clothing. Smoking history was

converted to pack years where one pack year is the equivalent of smoking one pack of 20 cigarettes daily for one year.

From the patient interview and medical records, we obtained general data including age, sex, height, weight, smoking history, performance status modified by Eastern Cooperative Oncology Group [Bearhs et al, 1992], exercise capacity [Froelicher, 1994], dyspnea scale [Mahler et al, 1987], New York Heart Association Class [Cheitlin et al, 1993], and the presence of COPD, heart disease, other medical condition, or prior thoracic operation. Laboratory data including blood hemoglobin, serum albumin, creatinine, and glutamic oxaloacetic transaminase (GOT) were recorded. We reviewed cardiac investigation (electrocardiogram (EKG), echocardiogram, cardiac stress test), radiology findings including chest radiography and CT scan, and radionuclide lung ventilation/perfusion scan if it had been obtained for clinical evaluation. Following surgery, the patient was followed up and details of the operative procedure, postoperative complications, and duration of hospitalization were noted.

Spirometry

All the subjects had spirometry performed with a computerized dry rolling seal spirometer (Model no. 922; Sensormedics, Anaheim, CA or Model "Transfer Test USA"; PK Morgan, Chatham, Kent, UK). Subjects were required to inspire maximally, then forcibly blow the air out as fast and quickly as possible until the lungs were empty. The subjects then inspired maximally and fully to obtain a flow-volume loop. Spirometry was performed according to the

current ATS criteria [ATS, 1995], to obtain two best tests with FEV1 and FVC within 5%. The best FVC and FEV1 were selected, and the prediction equations of Crapo et al. [Crapo et al, 1981] were used to determine percent of predicted FEV1, FVC, and FEV1/FVC.

Lung volume measurements

Lung volumes and conventional SB-DLCO were measured in all subjects as part of their clinical evaluation. These measurements were not generally repeated specifically for the study if they had been done in the previous month. Functional residual capacity (FRC) was measured by the helium dilution technique (Model "Transfer Test USA"; PK Morgan, Chatham, Kent, UK). This technique involves the subjects rebreathing test gas with a helium mixture in a closed circuit until equilibration is reached, while helium concentration is continuously monitored with a helium analyzer. Throughout the six or seven minutes duration of the test, CO2 is removed by a soda-lime absorber, and O2 is added. At the end of the helium dilution technique, the subject performs two slow vital capacity maneuvers. Based on the degree of helium dilution, the volume of the lungs at the resting end-expiratory level is determined (FRC). TLC is calculated from FRC and the inspiratory capacity (IC), while RV is calculated from FRC and expiratory reserve volume. Prediction equations for normal lung volumes were those of Crapo [Crapo et al, 1982].

DLCO

DLCO was measured by the single breath technique [Ogilvie et al, 1957] using an

automated valve and timing device and a bag in a box system (Model "Transfer Test USA"; PK Morgan, Chatham, Kent, UK). The subject inspired a volume of test gas containing 10% He, 0.3% CO, 21% O2, and the balance N2. SB-DLCO was measured according to standard technique [ATS, 1995] using a 10 second breath-holding time, determined by the Jones and Meade method [Jones and Meade, 1961]. The dead space washout and alveolar sample collection were set at 900 ml, and were reduced to 750ml in patients with FVC < 2.2 L. The alveolar sample passed through canisters containing soda-lime and anhydrous calcium sulphate to remove CO2 and water vapour, respectively, before passing through the He and infrared CO analyzers. All subjects were encouraged to relax and avoid exerting any inspiratory or expiratory effort during breath holding. The mean of the two DLCO measurements which agreed to within 5% of each other, was taken to indicate SB-DLCO. In order to satisfy this criteria, a maximum of four DLCO maneuvers, separated by at least 4 minutes, might have been performed. SB-DLCO was calculated by the computerized Morgan equipment according to the following equation [ATS, 1995]:

$$\text{SB-DLCO} = V_A*(\text{STPD correction})*(60/t)*(1/P)*\ln[(F_ICO*F_EHe)/(F_ECO*F_IHe)] \quad [6]$$

where SB-DLCO is the pulmonary diffusing capacity for CO (ml of CO*min^{-1}*mmHg^{-1}), V_A is the single breath alveolar breath holding volume at ambient pressure and temperature in ml and is calculated from VC and the inspired and expired helium concentrations, STPD correction is to change the volume to standard pressure (760 mmHg) and temperature (0°C) dry, F_IHe and F_EHe are the inspired and expired fractional concentrations of He respectively, F_ICO and F_ECO are the inspired and expired fractional concentrations of CO respectively, P is the total alveolar gas

pressure (P = barometric pressure-water vapour pressure), t is the breath holding time in seconds, and 60 is to convert the seconds to minutes. Predicted values for DLCO were derived from the prediction equation of Miller et al for non-smokers [Miller et al, 1983].

3EQ-DLCO EQUIPMENT

Breathing apparatus

A schematic diagram of the breathing apparatus is provided in Figure 2. The subjects breathed from a mouthpiece (with sputum trap) attached to a three way sliding Hans Rudolph valve (Model no. 2870; Hans Rudolph, Kansas City, MO). This three way sliding Hans Rudolph valve could be switched either to a two way Hans Rudolph valve (Model no. 2700; Hans Rudolph, Kansas City, MO), or to the 3EQ-DLCO system. The two way Hans Rudolph valve had inspiratory and expiratory ports to room air. The 3EQ-DLCO circuit consisted of two one-way valves to separate inspired and expired circuits. The inspiratory one-way valve led to a non-mixing switching valve, which allowed the subject to inspire either test gas from the inspiratory bag in a sealed Plexiglas box, or room air from the box. The expiratory one-way valve emptied into the expired bag in the box. The dead space of the equipment was kept to a minimum because an increased dead space will increase the response time of the 3EQ-DLCO system. A #3 Fleisch pneumotach connected to a $\pm$2 cmH2O differential pressure transducer (Model "MP45-14-871"; Validyne, Northridge, CA) was attached to the box to measure all flow in and out of the bags or box. Only ambient room air flows through the pneumotach. Linearing tubes that are six times

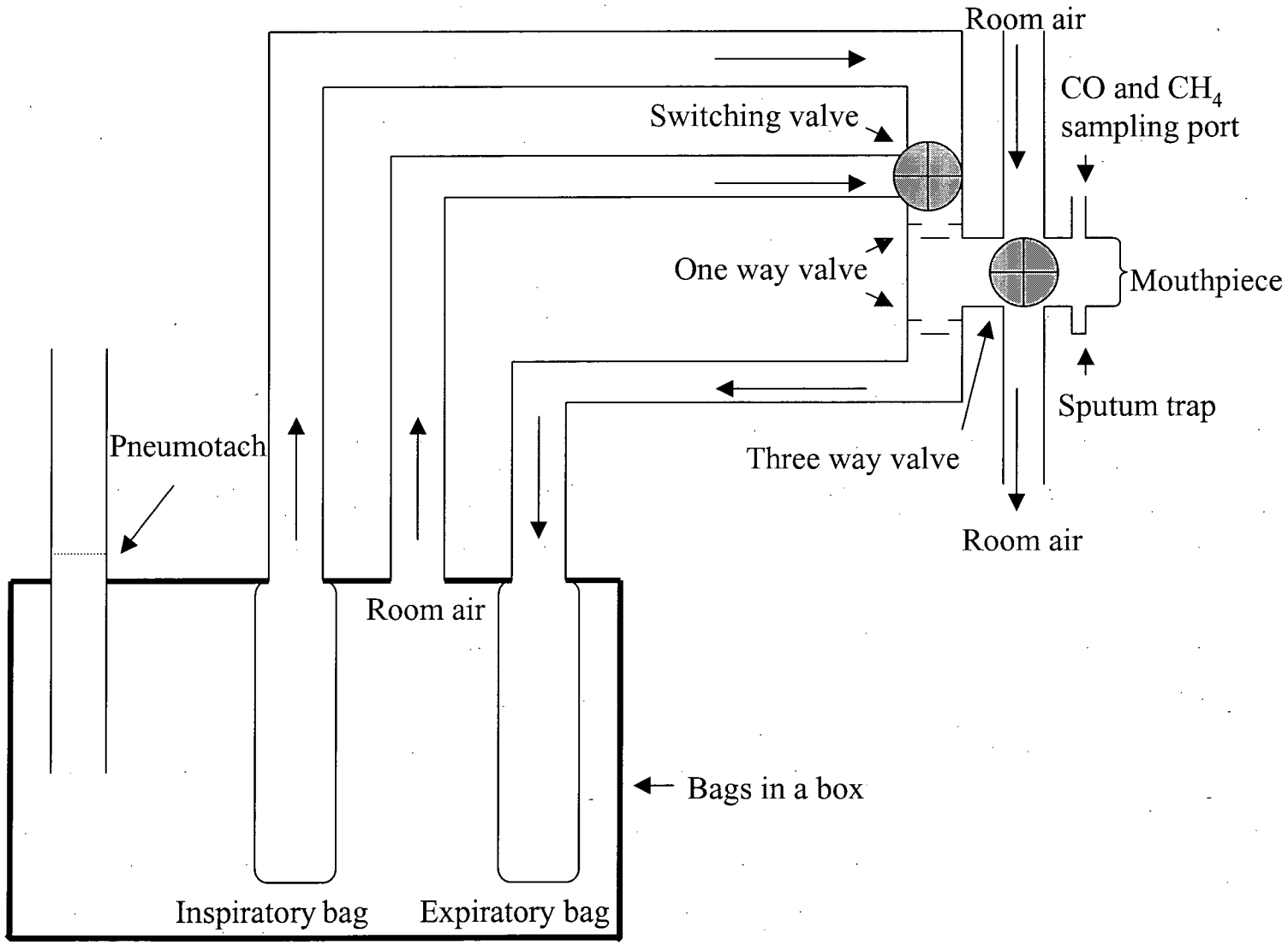

Figure 2. The breathing apparatus for the 3EQ-DLCO system. The three way valve could be switched to the 3EQ-DLCO system or a two way valve communicating with room air in both ends.

longer than the diameter of the pneumotach are used to maintain a uniform flow profile in and out of the pneumotach. The pneumotach output was amplified in a carrier demodulator (Model "CD15"; Validyne, Northridge, CA) and the flow signal was integrated by the computer software to determine volume. A gas sampling port located just distal to the mouthpiece, was used to sample gas at a rate of 100 ml/s through the rapidly responding gas analyzers by a vacuum pump (Model no. 8805; Sargeant-Welch, Skokie, IL). It was important to ensure the system was free from leaks; with low gas concentrations and high aspiration rates, a small leak could make a significant difference in the signal. Water vapour was removed from the sample gas by using Permapure© tubing (Model "MD-110-72E"; Permapure Inc., Toms River, NJ) which is selectively permeable only to water and which was kept dry by flushing its exterior with dry O_2. This was done with the use of an external jacket of hard plastic tubing surrounding the Permapure tubing through which dry O_2 was continuously flushed.

Gas analysers

The three-equation technique requires continuous measurements of CO and inert tracer gas concentrations with rapid response gas analyzers. Traditionally, He, analysed by a mass spectrometry, has been used as the tracer gas, but CH4 can be substituted instead, and has been used in measurement of SB-DLCO with commercial equipment [Ramage et al, 1987; Huang et al, 1992]. The solubility of CH4 in water at 37°C is 2.18×10^{-5} as compared to 6.99×10^{-6} for He. The slightly greater solubility of CH4 may lead to an overestimation of lung volume; however, the predicted effect is negligible [Huang et al, 1992]. Infrared absorption gas analyzers (Model

"BINOS® IR Gas Analyzer"; Leybold-Heraeus, Hanau, Germany) were used to measure CO and CH4 levels throughout the 3EQ-DLCO maneuver. The response time of the gas analysers was critical because a slow response time makes significant errors in the 3EQ-DLCO measurement [Graham et al, 1996]. The response time of the gas analyzer is dependent on the chamber size, sampling rate, the gas pressure in the sample cell, and the geometry of the system [Graham et al, 1996]. Increasing the sampling rate improves the response time of the gas analyzer, but reduces the density of test gas in the chamber, hence decreasing the signal to noise ratio. Similarly, using a small sample chamber will increase response time, but will also decrease the signal to noise ratio. An optimal signal is a balance between response time and signal to noise ratio. A moderate sampling rate of 100 ml/s produced a 0-90% response time of 250 ms with our analyser; this sampling rate and response time were considered acceptable for our experimental protocol [Potts et al, 1996; Rai et al, 1998], and would lead to < 1% error in DLCO [Graham et al, 1996]. The lag time of the gas analyzer is the transport time elapsed from the sampling port on the mouthpiece to the sampling chamber in the gas analyzer. This value was calculated and added to the response time of the gas analyzers in the processing of the data by the computer software. The lag and response times were checked regularly and the gas analyzer response time was verified to be under 250 ms (Appendix VI).

Data acquisition

The CO concentration, CH4 concentration, and flow analog signals were filtered with a 10Hz low pass filter and sampled at a rate of 50 Hz per channel. A 12-bit analog to digital

converter (Model "STA08-PGA"; Keithley Metrabyte, Taunton, MA), with its full range adjusted to match the signal amplitude, was used to digitize the signal before subsequent computer processing. We used a personal computer with a 386 processor and a customized QUICKBASIC (Microsoft Corp., WA) software program containing the three-equation algorithm (kindly provided by Dr. Brian L. Graham, University of Saskatchewan, Saskatoon). This algorithm calculates DLCO using a reiterative techniques; first the predicted DLCO is used to calculate the mean exhaled CO concentration [CO]. The calculated [CO] is then compared with the measured [CO], and if not matched, another value of DLCO is used to calculate [CO]. The bisection method finds an upper and lower bound for DLCO and uses the midpoint for successive iterations. If the initial value for DLCO is too low, then calculated [CO] will be higher than measured [CO]. So predicted DLCO becomes the lower bound and doubled predicted DLCO becomes the upper bound. Conversely, if the initial value for DLCO is too high, then calculated [CO] will be lower than measured [CO]. So predicted DLCO becomes the upper bound and 0 becomes the lower bound. A new DLCO is determined by the mean of the upper and lower bound values. The new DLCO is then used to calculate [CO], which is compared with measured [CO] to determine whether new DLCO is too high or too low. This process is repeated until calculated [CO] is within 0.1% of measured [CO]. In most instances, 12 or fewer iterations are required to converge to the solution for DLCO.

CALIBRATION OF 3EQ-DLCO EQUIPMENT

Flow meter

The pneumotach was checked by using a rotameter system for linearity within 1% of full

scale over a flow range of 0.5 l/s to 3 l/s for both inhalation and exhalation. Any nonlinearity was corrected with digital signal processing. On a daily basis, the flow signal was calibrated with a 3 liters syringe without the gas analyzers aspirating any gas. The integrated volume during expiration and inspiration was verified to be within 1% of the actual syringe volume at the same flow range. The aspiration pump was turned on, and the pneumotach calibration was repeated while gas was being aspirated through the analyzers. A significant day to day change in the gas analyser aspiration rate indicated the need to check a blockage, malfunction, or leak in the system. Again the inspiratory and expiratory volumes were verified to be within 1% of 3 liters. This second calibration allowed for the measurement of the flow signal caused by the aspiration of the gas analyzers. This constant gas analyzer aspiration flow signal was used to offset the flow signal during actual breathing maneuvers, effectively compensating for the gas aspiration flow rate. Any detectable flow would then be attributed to the breathing maneuver itself. When the exhaled flow rate of the subject fell below the aspiration rate of the gas analyzers, the gas analyzer measurements were considered to be meaningless, since there would be contamination with air.

Gas analysers

The gas analyzers were calibrated against direct sampling of tank gas (PRAXAIR Canada Inc., Mississauga, ON) containing known test gas concentrations of CO (0.30%$\pm$0.02) and CH4 (0.30%$\pm$0.02). Before daily use, the output of the CO and CH4 analyzers were checked for

linearity for both gas analyzers simultaneously by determining CO and CH4 concentration at different dilutions of the inspired gas mixture with room air. A graph of the CO and CH4 concentrations at these different dilutions was then plotted to ensure that the gas concentrations remained linear at the different concentrations. The response time and lag time were checked periodically. The effectiveness of the Permapure tubing in removing water vapour from the expired gas samples was checked periodically by determining that there was no difference in results between inspired CO/CH4 concentrations from the tank before and after humidifing the gas sample with a nebulizer.

IMPLEMENTATION OF 3EQ-DLCO

Verifying procedures

Before and after any breathing maneuvers, the average zero levels of CO, CH4, and the pneumotach were determined for each signal over 2 seconds with the gas analyzers aspirating room air and pneumotach occluded. This value was taken to be the "dry zero" with no CO2 or water vapour; the "dry zero" included the theoretical interfering effect of any ambient CO which would be negligible. To ensure adequate washout had occurred from the last test, the CH4 concentration was measured when the subject first breathed through the mouthpiece. If the CH4 concentration was > 1% of the inspired CH4 gas within the first three tidal breaths, then the test was rejected. If the gas analyzer zero drifted by more than 20 parts/million, or if the flow zero drifted more than 10 ml/s before and after the breathing maneuver, then the 3EQ-DLCO

measurement was rejected.

Breathing maneuver

Subjects were seated upright for all 3EQ-DLCO maneuvers. After being switched into the 3EQ-DLCO system, subjects were requested to follow a previously selected template of the breathing maneuver on a computer monitor, to guide subjects through the maneuver (Figure 3). The template was the same shape in all subjects, but the relative magnitudes of the inspiratory and expiratory segments were based on the subject's FRC, IC, and VC, which were entered in the computer software. Flow rates were set from 0.5 l/s to 2.5 l/s depending on the breathing capabilities of the subjects. The slope of the lines on the template allowed the subject to adjust inspiratory and expiratory flow rates, and breath holding time. The first breathing maneuver consisted of a deep inspiration of room air from FRC to TLC, a brief breath holding, and an expiration to FRC. The purpose of this first phase was to control volume history and to determine the "wet zero" during the expiration. The "wet zero" is different from the "dry zero" in that it includes interfering effects of residual background CO (from smoking, environmental exposure, or previous DLCO tests), exhaled CO_2, and water vapour left after Permapure tubing drying. This "wet zero" compensated for the back pressure of CO, which could be a significant factor when analyzing serial maneuvers. The "wet zero" also corrected for any minimal interfering effect of expired CO2 or the CO analyzer signal during exhalation phase of the second breathing maneuver, which involved inhalation of the test gas from the inspiratory bag containing 0.3% CO, 0.3% CH4, 21% O2, and balance nitrogen. Subjects inhaled the test gas from FRC to TLC,

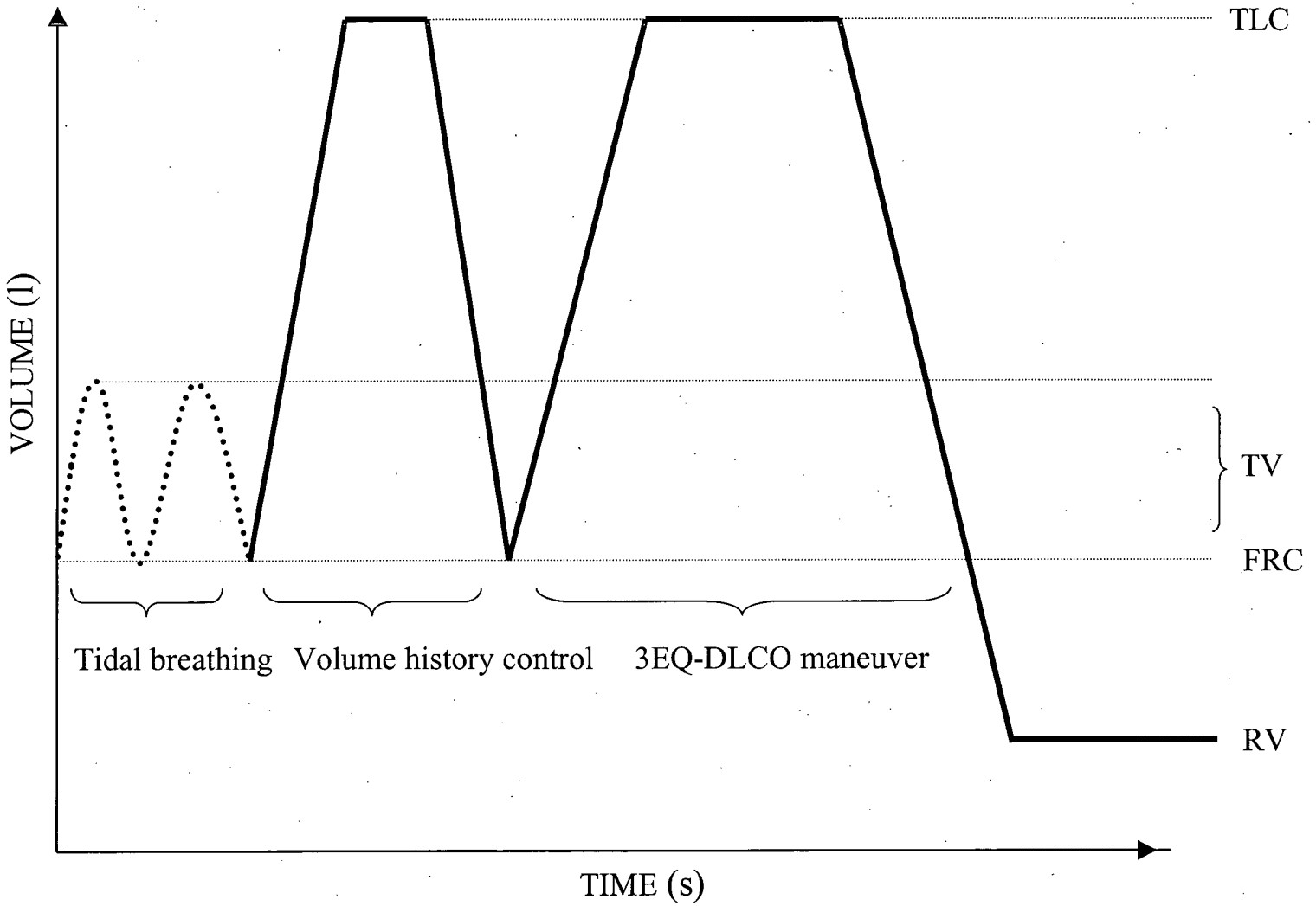

Figure 3. The breathing template for 3EQ-DLCO maneuver. At the end of tidal breathing, the subject inhales room air from FRC to TLC with brief breath-holding, then exhales to FRC, for the volume history control. The subject then inhales test gas from FRC to TLC with breath-holding for about 2 s, then exhales to RV, for the 3EQ-DLCO maneuver. TLC=total lung capacity; TV=tidal volume; FRC=functional residual capacity; RV=residual volume.

held their breath for about 2 seconds, and exhaled to RV.

Data Analysis

The flow signal was integrated to derive volume. The gas analyzer signals in the inspiratory and expiratory phases of the actual 3EQ-DLCO single breath were compared with the "dry zero" and the "wet zero", respectively. The raw CO and CH4 gas analyzer outputs and the volume signals were used to construct washout curves for CO and CH4 concentrations versus volume. The CH4 washin and washout curves were used respectively to determine the amount of tracer gas inhaled and the amount of tracer gas exhaled to determine how much tracer gas remained in the lung at RV; the lung volume at RV is then calculated assuming end expired [CH4] is equal to mean alveolar [CH4] at RV [Graham et al, 1985]. The RV was added to the VC, determined from the volume signal, to obtain TLC. The anatomic dead space was determined using a computerized algorithm based on the Fowler method [Fowler, 1948], using the CH4 washout instead of nitrogen washout. This measurement of dead space included the equipment dead space between the gas analyzer sample port and the mouthpiece. Alveolar lung volume was calculated by subtracting the dead space from total lung volume. The point of dead space washout for CO was determined by first dividing the CO washout curve into three equal sections by volume (Figure 4), and a linear regression line through the middle third was drawn. The point at which the exhaled CO concentration first crossed this line was taken to be the point of dead space washout. The washout volume was the volume exhaled from the TLC to this point. The largest exhaled alveolar gas sample for analysis begins at the point of dead space washout

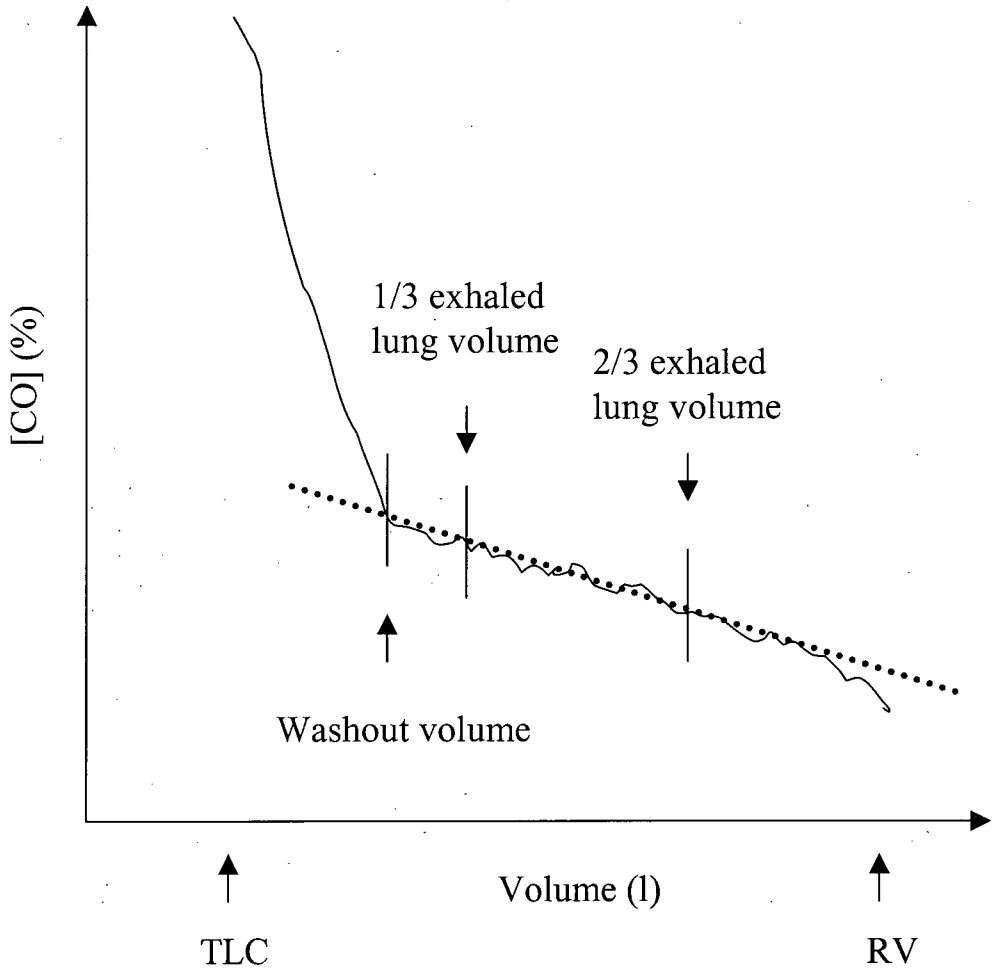

Figure 4. The washout curve of CO. The point of dead space washout is measured from the intersection of the CO concentration washout curve with a linear regression line through the middle third (by volume) of exhaled CO versus lung volume. TLC=total lung capacity; RV=residual volume.

and continues to end-exhalation. The main advantages of using the largest possible exhaled gas sample are the estimate of DLCO will be more representative of the entire lung and the measurement of total lung volume will similarly be more accurate. The predicted [CO] calculated by the three-equation algorithm using an assumed DLCO is compared with the measured [CO], and an iterative technique is then used to calculate 3EQ-DLCO, which is considered to be the correct value when calculated [CO] agrees with measured [CO] to within 0.1%.

Reproducibility of 3EQ-DLCO

Prior to the study, the reproducibility of 3EQ-DLCO measurements at rest and during different levels of steady state exercise were tested in 6 normal, healthy volunteers on 2 separate days. The mean 3EQ-DLCO was 39.91±1.78 ml/min/mmHg at rest and 52.86±2.09 ml/min/mmHg at 70% of maximal workload on the two separate days; the mean coefficient of variation of 3EQ-DLCO was 4.5% at rest and 4.0% during steady state exercise.

PROGRESSIVE EXERCISE TESTING EQUIPMENT

All exercise was performed on a computerized cycle ergometer (Model "SensorMedics 800"; SensorMedics, Anaheim, CA). The subjects with nose clip applied breathed through a rubber mouthpiece attached to a sputum trap. A headgear was used to support the mouthpiece connected to a detachable mass flow sensor (Model "Vmax/V6200"; SensorMedics, Anaheim, CA). The inspired and expired gases were sampled continuously at the mouth, and dried with

Permapure tubing before entering the gas analyzers. Oxygen concentration was measured using a rapidly responding paramagnetic oxygen analyzer, and CO2 concentration with an infrared analyser (Model "Vmax 229"; SensorMedics, Anaheim, CA). The heart rate and electrocardiogram were monitored continuously by a 12-lead EKG monitor (Model no. 4000; Quinton, Seattle, WA), and O2 saturation was monitored by pulse oximetry (Model "S-100e"; SiMed, North Bothell, WA). All the signals were sampled real-time breath-by breath and the output stored through Pulmonary Function/Cardiopulmonary Exercise Testing System (Model "Vmax 229"; SensorMedics, Anaheim, CA) into a personal computer with a 586 microprocessor. Metabolic and cardiopulmonary variables including minute ventilation, respiratory rate, O2 consumption, CO2 production, and respiratory exchange ratio were determined from the flow, O2, and CO2 signals and shown on-line on the monitor during exercise. The exercise equipment was calibrated and verified daily. For details of the exercise equipment calibration, refer to Appendix VII.

EXPERIMENTAL PROTOCOL

On the first day of experiment, subjects read and signed the informed consent form. The physicians examined the subject and filled in the clinical questionnaire. Spirometry, lung volume measurements, and SB-DLCO study were performed and compared with any prior results.

3EQ-DLCO at rest

Subjects rested in a seated position for 15 minutes prior to any diffusion capacity measurements to minimise the effect of any prior activity on DLCO. To familiarize the subjects with the breathing template, several practice runs of the breathing maneuver were performed with the subjects breathing room air from the bag in box system; flow rates were adjusted according to the lung function of the subjects. This process was repeated until the subject's breathing pattern sufficiently matched the flow rates and breath holding time of the breathing template on the computer monitor. A sample of test gas was then introduced into the inspiratory bag and the 3EQ-DLCO measurements were determined. Three 3EQ-DLCO measurements were measured at least 5 min apart; the mean of the three measurements which agreed to within 10% of each other was taken as the resting 3EQ-DLCO.

Progressive exercise testing

Maximum exercise capacity was determined by an incremental exercise test on a computerized cycle ergometer according to the routine protocol at the lung function laboratory. The exercise procedure was explained to the patients, and a supervising licensed physician was present during all exercise testing. EKG electrodes were applied for cardiac monitoring during exercise, and a 12-lead EKG tracing was obtained at rest. A vasodilator ointment, Finalgon© (0.4% nonylic acid vanillylamide and 2.5% beta-butoxyethyl ester of nicotinic acid; Boehringer Ingelheim, Burlington, Ontario, Canada), was applied sparingly to the ear lobe to improve blood flow. A pulse oximeter probe was applied to the ear, and a good pulse correlation between the EKG monitor and the oximeter was confirmed. If the ear oximeter probe did not provide an

accurate reading, a finger probe on the index finger was used. The seat height of the ergometer was adjusted so that the patient was able to cycle completely. Blood pressure was measured prior to exercise and periodically during exercise. The subjects were asked to breathe quietly through the mouthpiece with a nose clip applied while resting measurements were made for 3 minutes.

The subjects were then asked to start pedaling at about 60 revolutions per minute at a workload of 15 watts. The load was increased in steps of 15 watts every minute; after about 45 seconds at each workload, subjects were asked to indicate their perceived effort for breathing and cycling, on the Borg scale [Borg, 1982]. The exercise test was discontinued when the subject reached 90% of the maximal predicted heart rate, or felt fatigued and unable to continue, or if an abnormal EKG developed, or if the O2 saturation fell below 85%. At termination of exercise, the workload was reduced to zero, the mouthpiece and nose clip were promptly taken off, and the subjects pedaled freely for a few minutes till the heart rate decreased to about 100 min, to prevent venous pooling of blood in the lower extremities. If the subject desaturated, O2 was administered with a mask or nasal cannula. The maximal VO2 attained was taken to be the highest O2 consumption at the highest workload, just before the exercise test was discontinued. The predicted maximal VO2 in absolute amount and expressed by per kg of body weight were determined using the equations of Jones [Jones, 1997]. The maximal predicted heart rate was calculated by subtracting two-thirds the age of the subject from 210 [Jones, 1997].

3EQ-DLCO during steady state exercise

Our intent was to have the subjects perform steady state 3EQ-DLCO measurements on a separate day; however, for subjects unable to return on another occasion, the steady state exercise measurements were made on the same day. Subjects took a rest for at least 30 minutes after the progressive exercise testing to recover, before they proceeded to the final portion of the study, the evaluation of 3EQ-DLCO during steady state exercise.

Testing was done with the subjects seated on the cycle ergometer; blood pressure by a sphygmomanometer and O2 saturation by a pulse oximetry were monitored. All the subjects were asked to pedal on the cycle ergometer for 1 minute to warm up, and then the workload was increased to 35% of the premeasured maximal workload. A constant pedaling rate at this workload was maintained for 3 minutes, and then 3EQ-DLCO was determined while the subject continued to pedal. The workload was then increased to 70% of the premeasured maximal workload for another 3 minutes. At the end of 3 minutes of this higher workload, the steady state 3EQ-DLCO was determined. After another minute of pedaling, another 3EQ-DLCO was made. If at any point of the test subjects experienced severe dyspnea, tachycardia (> 90% of maximal predicted heart rate), desaturation (< 85%), or ECG change, the test was discontinued. After the DLCO determinations, subjects pedaled freely on the ergometer for a few minutes to allow their heart rate to normalize. Then, they came off the ergometer and recovered in a seated position.

In a few cases, after a single 3EQ-DLCO measurement at the higher workload, the subjects could no longer continue exercising long enough to repeat the 3EQ-DLCO test. These subjects were allowed to recover before another attempt was determined. Once recovered the

subjects started pedaling directly at the higher workload following warm up for 1 minute. After 3 minutes at the same workload, the second 3EQ-DLCO measurement was determined.

It was not feasible to determine VO2 during steady state exercise routinely just prior to the exercise 3EQ-DLCO tests. In selected subjects, VO2 was determined during steady state exercise at the two workloads just prior to the steady state 3EQ-DLCO measurements. These subjects were requested to breathe through the mouthpiece of the exercise testing system 30 seconds prior to the 3EQ-DLCO measurement while ventilation and gas exchange were monitored to determine VO2. The subjects were then switched to the mouthpiece of the 3EQ-DLCO system for the exercise 3EQ-DLCO determination. In these subjects, the VO2 at 35% of maximal workload during the steady state exercise (760$\pm$206 ml/min) was compared with the VO2 at the same workload during the progressive exercise testing (623$\pm$127 ml/min, $p<0.001$); the VO2 at 70% of maximal workload during the steady state exercise (1091$\pm$227 ml/min) was compared with the VO2 at the same workload during the progressive exercise testing (957$\pm$206 ml/min, $p<0.001$) (Figure 5). The ratio of the VO2 during steady state exercise to the VO2 during the progressive exercise testing at the lower level of exercise was 1.22$\pm$0.12 and at the higher workload was 1.14$\pm$0.09. In the other subjects who did not have determinations of VO2 during steady state exercise, these two ratios were used to convert the VO2 during progressive exercise testing to obtain VO2 during steady state exercise at the lower and higher workloads, respectively.

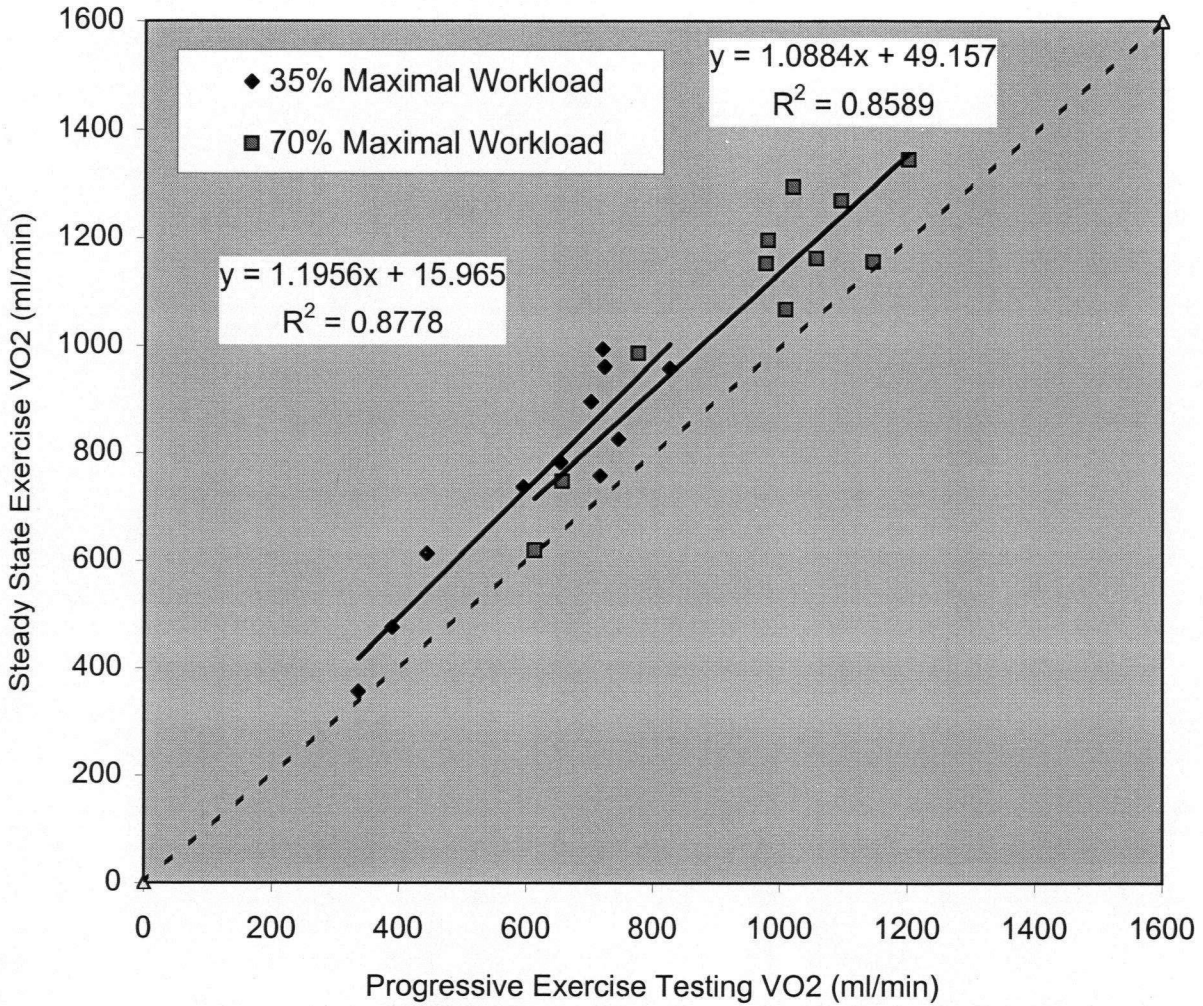

Figure 5. Comparison of VO2 determined during steady state exercise and during progressive exercise testing at the same workload. VO2 during steady state exercise was obtained from 11 patients at 2 different levels of maximal workload.

EVALUATION OF COMPLICATIONS FOLLOWING LUNG RESECTION

All thoracotomies and pulmonary resections were performed by either Drs. Kenneth G. Evans or Richard J. Finley, thoracic surgeons at Vancouver General Hospital. The postoperative course of the patients was followed carefully by myself, with detailed assessment and recording of complications. Postoperative complications during the patients' hospitalization after resection were classified into mortality, cardiovascular and pulmonary morbidity. Cardiovascular morbidity included myocardial infarction (based on symptoms and electrocardiogram change or cardiac enzyme elevation), congestive heart failure (requiring therapy), pulmonary edema (chest radiograph evidence), shock (systolic blood pressure < 90 mmHg), arrhythmia (requiring therapy), and cerebrovascular accident (brain CT evidence). Pulmonary morbidity included ventilatory support (> 48 hours), reintubation, pulmonary embolism (lung scan or pulmonary angiographic evidence), pneumonia (fever, leukocytosis, purulent sputum, and chest radiograph evidence), atelectasis (chest radiograph evidence, disappearing with respiratory therapy or therapeutic bronchoscopy), and respiratory insufficiency (arterial partial pressure of CO2 > 65 mmHg or arterial partial pressure of O2 < 55 mmHg on room air).

STATISTICAL ANALYSIS

Analysis of the data was done using Microsoft Excel™ 97 and SPSS™ 8.0 through a personal computer 586; we determined the means and SD for the different variables in the whole group and in patients with and without complications. Comparisons between different groups for

continuous variables were made using a two-tailed Student's t test [Zar, 1999]. The Chi-square test was used for categorical variables [Zar, 1999]. Analysis of multiple variables using stepwise logistic regression [Daniel, 1999] was performed to investigate the relative usefulness of the combination of different variables for the prediction of postoperative complications. A p value <0.05 was considered to be statistically significant.

Receiver operating characteristic (ROC) curve [Mould, 1998] and Fisher's exact test [Zar, 1999] were used to define the best cut-off limits of the different variables in relation to postoperative complications, and sensitivity and specificity for each variable were determined. The area under the ROC curve (AURC) was estimated using the following algorithm:

AURC between 2 successive points=mean sensitivity*difference in (1-specificity) [7]

The total AURC is the sum of successive individual areas. The relative risk, risk difference, and odds ratio [Joubert, 1997] in the preoperative evaluation, by using a given cut-off limit, were calculated as "A(C+D)/C(A+B)", "A/(A+B)-C/(C+D)", and "AD/BC"; the definition of the symbols is shown in Table I.

Table I. Definition of symbols used to calculate different cut-off limits from Fisher's exact test

	Complications	No Complications
< cut-off limits	A	B
≥ cut-off limits	C	D

CHAPTER THREE: RESULTS

SUBJECT RECRUITMENT

We attempted to recruit all suitable patients with lung cancer scheduled for lung resection at Vancouver General Hospital, through the outpatient clinics of the 2 thoracic surgeons at Vancouver General Hospital, and through the lung function laboratory at Vancouver General Hospital. Patients with inoperable advanced stage and patients scheduled for minimal invasive surgery (thoracoscopy) were not considered as candidates for our study. Out of eligible patients over the period of October 1st 1998 to May 31st 1999, we were able to recruit 65 patients. Of the patients considered suitable for the study, 7 patients were shown to have advanced cancer by mediastinoscopy and did not have thoracotomy, and 1 patient refused to have lung resection. When these 8 patients were compared with the 57 patients who had thoracotomy, no significant differences were found in their preoperative evaluation. The patients we studied were scheduled for lobectomy, or a more extensive resection, but a total of 13 patients had only segmentectomy, or wedge resection, or thoracotomy without resection, after surgical exploration.

SUBJECT CHARACTERISTICS

The 57 cases studied, had a mean age of 64±10 years; 39 (68%) were men, and 18 (32%) were women. Mean height was 170±10 cm, and weight was 74±15 kg. Twenty four patients

(42%) were smokers with a mean smoking history of 55±30 pack-years, and 22 (39%) were exsmokers with a mean smoking history of 34±24 pack-years. Eleven patients (19%) had never smoked. Review of medical history revealed that 24 patients (41%) had a diagnosis of COPD, 14 (25%) hypertension, 8 (14%) coronary artery disease, and 6 (11%) had prior chest operation. The questionnaire indicated that 51 patients (89%) fit the New York Heart Association class 1, 30 (53%) had performance status 1, 30 (53%) had exercise capacity 2, and 29 (51%) had dyspnea scale 1. Laboratory data revealed mean hemoglobin of 131±17 g/L, albumin 37±6 g/L, GOT 26±11 U/L and creatinine 87±17 umol/L. The chest radiograph showed a mass ($\geq$ 3cm in diameter) in 29 patients (51%), a nodule in 25 (44%), and consolidation in 3 (5%); in 30 patients (53%) the lesion was on the right, and in 27 (47%) on the left. One patient (2%) had an abnormal EKG (left bundle branch block) at rest, while 6 (11%) had an abnormal exercise EKG (left bundle branch block in 1 and ventricular premature contraction in 5).

The surgical interventions performed were 10 pneumonectomies, 2 bilobectomies, 32 lobectomies, 6 segmentectomies, 4 wedge resections, and 3 thoracotomies without lung resection. In 43 patients (75%), thoracotomy was through the 5th intercostal space, in 1 it was through the 3rd, in 6 it was through the 4th, and in 7 it was through the 6th. Pericardial dissection was performed in 4 patients (7%). The mean hospital stay was 10±3 days. Forty four patients (78%) had primary lung cancer, and 12 (21%) had stage 2B cancer. The most common cell types were adenocarcinoma and squamous cell carcinoma in 18 patients (32%) each, while 8 (14%) had undifferentiated carcinoma. Seven patients (12%) were found to have benign lesions on the

final pathology of the resected lung. There were 6 patients (11%) with metastatic cancer of various types.

Preoperative lung function data are shown in Table II. Mean FVC% predicted was 93±16%, but some patients had mild restrictive ventilatory impairment. Mean FEV1/FVC was 70±11%; some patients had mild or moderate obstructive ventilatory impairment. Mean DLCO% predicted was 78±19%, with some patients having mild or moderate diffusing capacity impairment.

Preoperative exercise and 3EQ-DLCO data are shown in Table III. Maximal exercise capacity was reduced in most patients, with a mean VO2max% maximal predicted of 66±14%. Mean O2 saturation by pulse oximetry was 94±3% (range from 87 to 98%) at rest, and decreased by a mean of 1±2% (range from –8 to 8%). To adjust for differences in sex, age, and height on different subjects, 3EQ-DLCO at rest and exercise was expressed as % predicted of resting SB-DLCO. Mean 3EQ-DLCO at rest (RDLCO) was 22.81±8.44 ml/min/mmHg, and RDLCO% predicted was 93±33%. Mean DLCO at 70% of maximal workload (70%DLCO) was 28.87±10.79 ml/min/mmHg, and 70%DLCO% predicted was 119±43%. Mean increase in 70%DLCO% predicted from RDLCO% predicted ((70%-R)DLCO%) was 25±18%, and there was a significant variability in the increase of 3EQ-DLCO with exercise.

COMPLICATIONS FOLLOWING LUNG RESECTION

Postoperative complications occurred in 19 patients (33%), and included mortality in 2

Table II. Preoperative lung function data

Variables	Mean ± SD (Range)	Mean ± SD% predicted (Range)
FEV1 (L)	2.51±0.66 (1.18 to 3.93)	83±19 (40 to 129)
FVC (L)	3.62±0.81 (1.75 to 5.12)	93±16 (65 to 130)
FEV1/FVC (%)	70±11 (50 to 90)	90±14 (60 to 131)
RV/TLC (%, n=47)	37±9 (22 to 61)	104±24 (63 to 177)
DLCO (ml/min/mmHg, n=47)	19.56±6.12 (9.52 to 42.95)	78±19 (42 to 114)
DLCO/VA (ml/min/mmHg/L, n=47)	3.67±1.05 (1.73 to 6.71)	85±20 (43 to 137)

Table III. Preoperative exercise and 3EQ-DLCO data

Variables	Mean ± SD (Range)	Mean ± SD% predicted (Range)
Maximal workload (watt)	108±32 (30 to 196)	80±28 (30 to 180)
VO2max (ml/min)	1314±381 (636 to 2632)	66±14 (36 to 101)
VO2max/kg (ml/kg/min)	18±4 (10 to 28)	74±15 (40 to 110)
Maximal O2 pulse (ml/beat)	9.8±2.6 (5.4 to 17.3)	77±18 (47 to 106)
3EQ-DLCO (ml/min/mmHg)	22.81±8.44 (6.10 to 45.22)	93±33 (27 to 169)*
70%DLCO (ml/min/mmHg, n=55)	28.87±10.79 (6.47 to 55.99)	119±43 (29 to 204)*
(70%-R)DLCO% (%, n=55)	25±18 (-9 to 59)*	NA
(70%-R)DLCO/VO2 (@, n=55)	6.9±5.2 (-2.4 to 18.8)	NA
(70%-R)DLCO/VO2% (n=55)	0.56±0.44 (-0.21 to 1.44)*#	NA

NA: not available; *: predicted for 3EQ-DLCO is % predicted of resting SB-DLCO; @: (ml/min/mmHg)/(L/min); #: predicted for VO2 is % predicted of maximal VO2.

(4%), cardiovascular morbidity in 12 (21%), and pulmonary morbidity in 13 (23%)(Table IV). The causes of the 2 deaths were pulmonary edema. Arrhythmia (atrial fibrillation in 10 patients and ventricular premature contraction in 1 patient) was the major cause of cardiovascular morbidity occurring in 19% of all patients. Two patients had pulmonary edema and 1 shock. Pneumonia was the major cause of pulmonary morbidity occurring in 7 patients (12% of all cases). Five patients had atelectasis, 4 developed respiratory insufficiency, and 2 required ventilatory support and reintubation.

CLINICAL EVALUATION

Clinical evaluation completed on all subjects, was compared in patients with complications and those without complications (Table V). Patients with complications were older than those without complications, and were more frequently diagnosed with COPD; they had worse dyspnea scale, less exercise capacity, and poor performance status, but there was no difference in New York Heart Association classification. There were no differences in height, weight, sex distribution, and smoking status or cigarette consumption between the two groups. Among the 19 patients with complications, there were 5 patients with a history of hypertension, 2 with coronary heart disease, and 2 with prior chest operation, while among the 38 patients without complications, there were 9 with a history of hypertension, 6 with coronary heart disease, and 4 with prior chest operation; there were no statistically significant differences between the 2 groups. There was no difference between the 2 groups in the type of lesion by chest radiography, or in blood laboratory tests (blood hemoglobin, albumin, creatinine, and

Table IV. Prevalence of postoperative complications following lung resection

Results	Percentage (n=57)
Overall complications	33% (19)
Mortality	4% (2)
Cardiovascular morbidity	21% (12)
Myocardial infarction	0% (0)
Congestive heart failure	0% (0)
Pulmonary edema	4% (2)
Shock	2% (1)
Arrhythmia	19% (11)
Cerebrovascular accident	0% (0)
Pulmonary morbidity	23% (13)
Ventilatory support	4% (2)
Reintubation	4% (2)
Pulmonary embolism	0% (0)
Pneumonia	12% (7)
Atelectasis	9% (5)
Respiratory insufficiency	7% (4)

Table V. Clinical evaluation in relation to complications

Variables	Complications (n=19)	No Complications (n=38)	p value
Age (yr)	70±6	61±11	<0.01
Chronic obstructive pulmonary disease (Y/N)	14/5	10/28	<0.01
New York Heart Association class (1/2)	18/1	33/5	NS
Dyspnea scale (0/1/2)	4/14/1	23/15/0	<0.05
Exercise capacity (1/2)	4/15	23/15	<0.05
Performance status (0/1)	4/15	23/15	<0.05
Surgical procedure			<0.05
Pneumonectomy	6	4	
Bilobectomy	1	1	
Lobectomy	12	20	
Segmentectomy	0	6	
Wedge resection	0	4	
Thoracotomy	0	3	
Intercostal space for surgery (3/4/5/6)	0/5/11/3	1/1/32/4	<0.05
Final diagnosis			<0.05
Lung cancer	19	25	
Metastatic cancer	0	6	
Benign lesion	0	7	

NS: not significant.

GOT), or in EKG findings at rest or during exercise. There were no significant differences in staging between the 2 groups, or the duration of hospitalisation (11±3 days in the group with complications versus 10±3 days in the group with no complications). Thoracotomy through the 5th intercostal space was less often done in patients with complications, but there were no differences in the frequency of pericardial dissection. All patients with complications had primary lung cancer, while in those without complications, 6 had metastatic cancer and 7 had benign lesion. All patients with complications had more extensive lung resection, consisting of 6 pneumonectomies, 1 bilobectomy, and 12 lobectomies.

The two patients with mortality had more extensive lung resection ($p<0.01$), consisting of 1 pneumonectomy, and 1 bilobectomy. The 12 patients with cardiovascular complications were older (71± 6 versus 62± 10 yr, $p<0.01$) than those without cardiovascular complications, and had more extensive lung resection ($p<0.05$), consisting of 6 pneumonectomies, 1 bilobectomy, and 5 lobectomies. The 13 patients with pulmonary complications were older (70± 5 versus 62± 11 yr, $p<0.01$) than those without pulmonary complications, had worse dyspnea scale ($p<0.01$), less exercise capacity ($p<0.05$), and poor performance status ($p<0.05$), and more extensive lung resection, consisiting of 4 pneumonectomies, 1 bilobectomy, and 8 lobectomies.

LUNG FUNCTION TESTING INCLUDING DLCO

Spirometry was performed in all subjects, but lung volume measurements and DLCO were determined in 47. Lung function tests including DLCO were compared between patients

with complications and patients without complications (Table VI). Patients with complications had lower FEV1% predicted, FVC% predicted, FEV1/FVC, DLCO% predicted, and DLCO/VA% predicted, indicating mild obstructive ventilatory and diffusing capacity impairment.

Results of lung function tests were also related to the presence or absence of cardiovascular and pulmonary complications separately. Patients with cardiovascular complications had lower DLCO% predicted (60± 12 versus 83± 17%, $p<0.001$) than patients without cardiovascular complications, indicating mild diffusing capacity impairment. Patients with pulmonary complications had lower FEV1% predicted (68± 15 versus 88± 18%, $p<0.001$), FEV1/FVC (61± 10 versus 72± 10%, $p<0.01$), and DLCO% predicted (62± 14 versus 83± 17%, $p<0.001$) than patients without pulmonary complications, indicating mild obstructive ventilatory and diffusing capacity impairment.

PROGRESSIVE EXERCISE TESTING

All subjects had progressive exercise testing, and results were compared between patients with complications and patients without complications (Table VII). Patients with complications had lower maximal workload, VO2max, VO2max/kg, and O2 pulse at maximal workload, indicating moderate exercise capacity impairment.

Analysis of cardiovascular and pulmonary complications done separately showed that

Table VI. Preoperative lung function variables in relation to complications

Variables	Complications (n=19)	No Complications (n=38)	p value
FEV1 (L)	2.15±0.50	2.69±0.66	<0.01
FVC (L)	3.39±0.82	3.73±0.79	NS
FEV1% predicted	72±14	89±19	<0.001
FVC% predicted	87±16	97±15	<0.05
FEV1/FVC (%)	64±11	72±11	<0.05
RV/TLC (%)	40±8 (n=17)	36±9 (n=30)	NS
DLCO (ml/min/mmHg)	15.31±3.72 (n=17)	21.98±5.92 (n=30)	<0.001
DLCO% predicted	62±13 (n=17)	87±15 (n=30)	<0.001
DLCO/VA (ml/min/mmHg/L)	3.05±0.91 (n=17)	4.03±0.97 (n=30)	<0.01
DLCO/VA% predicted	74±23 (n=17)	91±17 (n=30)	<0.05

NS: not significant.

Table VII. Preoperative exercise and 3EQ-DLCO variables in relation to complications

Variables	Complications (n=19)	No Complications (n=38)	p value
Maximal workload (watt)	90±30	117±29	<0.01
VO2max (ml/min)	1095±300	1423±373	<0.001
VO2max% maximal predicted	57±14	70±13	<0.01
VO2max/kg (ml/kg/min)	15.0±2.4	19.2±4.3	<0.001
VO2max/kg% maximal predicted	70±14	76±15	NS
Maximal O2 pulse (ml/beat)	8.8±2.4	10.3±2.6	<0.05
3EQ-DLCO (ml/min/mmHg)	17.38±7.08	25.53±7.80	<0.001
3EQ-DLCO% predicted*	76±37	102±27	<0.05
70%DLCO (ml/min/mmHg)	18.77±7.36 (n=18)	33.78±8.56 (n=37)	<0.001
70%DLCO% predicted*	83±40 (n=18)	136±33 (n=37)	<0.001
(70%-R)DLCO% (%)*	5±9 (n=18)	34±14 (n=37)	<0.001
(70%-R)DLCO/VO2 (@)	1.7±2.7 (n=18)	9.4±4.1 (n=37)	<0.001
(70%-R)DLCO/VO2%*#	0.13±0.23 (n=18)	0.76±0.36 (n=37)	<0.001

NS: not significant; *: predicted for 3EQ-DLCO is % predicted of resting SB-DLCO; @: (ml/min/mmHg)/(L/min); #: predicted for VO2 is % predicted of maximal VO2.

patients with cardiovascular complications had lower maximal workload (89± 37 versus 114±28 watt, $p<0.05$), VO2max% maximal predicted (57± 16 versus 68± 13%, $p<0.05$), VO2max/kg (14.7± 2.9 versus 18.6±4.2 ml/kg/min, $p<0.01$), and O2 pulse at maximal workload (8.2± 2.3 versus 10.2± 2.6 ml/beat, $p<0.05$) than patients without cardiovascular complications, indicating mild exercise capacity impairment. Patients with pulmonary complications had lower maximal workload (90± 25 versus 114± 31 watt, $p<0.01$), VO2max% maximal predicted (55± 14 versus 69± 13%, $p<0.01$), and VO2max/kg (14.7± 2.0 versus 18.7± 4.4 ml/kg/min, $p<0.001$) than patients without pulmonary complications, indicating mild exercise capacity impairment.

3EQ-DLCO DURING EXERCISE

3EQ-DLCO at rest was measured in all patients, while DLCO at 35% of maximal workload was determined in 43 and DLCO at 70% of maximal workload in 55. Three measurements of 3EQ-DLCO at rest that agreed within 10% of each other were obtained and averaged. 3EQ-DLCO at rest was significantly greater ($p<0.001$) than the conventional SB-DLCO, both expressed as % predicted of resting SB-DLCO (93±33% versus 78±19%), especially when SB-DLCO was > 70% predicted (Figure 6). This difference was due to differences in the breathing maneuvers used in the two methods. In the 3EQ-DLCO technique, subjects breathe out to FRC prior to the inhalation of test gas, but in the SB-DLCO technique, they breathe out to RV prior to the DLCO test. Inhalation of test gas from FRC will increase 3EQ-DLCO values when compared with inhalation from RV [Cotton et al, 1992].

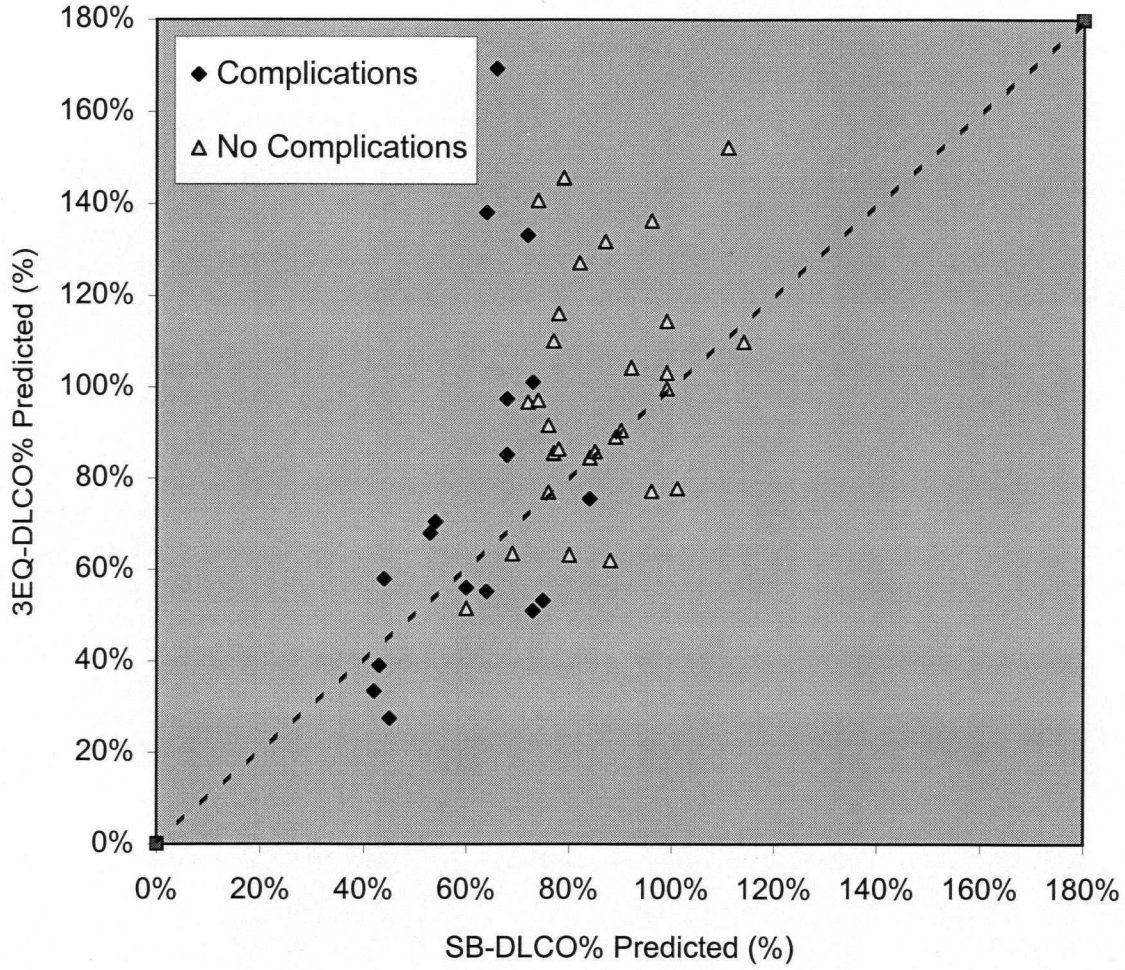

Figure 6. Comparison of DLCO determined by SB-DLCO and by 3EQ-DLCO methods in the same subjects. The mean of 3EQ-DLCO (93±33%) was significantly higher ($p < 0.001$) than that of SB-DLCO (78±19%) . The dotted line is the line of identity.

Our original protocol was to do progressive exercise testing and 3EQ-DLCO steady state measurements on separate days; however, most subjects were unwilling or were unable to come for the study on two different days. In these subjects, the steady state exercise 3EQ-DLCO was measured after at least 30 min of rest following the progressive exercise testing. The subjects were exercised at steady state workloads corresponding to about 35% and 70% of their maximal workload measured from the progressive exercise testing. The 3EQ-DLCO measurement was done as a single determination at the lower workload, but was done in duplicate at the higher workload. Four patients had maximal workloads equal to or less than 60 W and were only tested at the higher 70% workload. Two measurements of 3EQ-DLCO at 70% of maximal workload that agreed within 10% of each other were obtained and averaged.

The 3EQ-DLCO studies were compared between patients with complications and patients without complications (Table VII). Patients with complications had lower RDLCO% predicted, 70%DLCO% predicted, and (70%-R)DLCO%, indicating mild diffusing capacity impairment at rest and inadequate increase in DLCO during exercise.

The two mortality cases had lower 70%DLCO% predicted (75±7 versus 121±44%, $p<0.01$), and (70%-R)DLCO% (-1±5 versus 26±17%, $p<0.01$) than the surviving patients, indicating inadequate increase in DLCO during exercise. It is interesting that their lung function and maximal exercise data were within the range of the surviving patients. Patients with cardiovascular complications had lower 70%DLCO% predicted (89±47 versus 127±39%,

$p<0.05$), and (70%-R)DLCO% (6±10 versus 30±17%, $p<0.001$) than patients without cardiovascular complications, indicating inadequate increase in DLCO during exercise. Patients with pulmonary complications had lower RDLCO% predicted (71±29 versus 100±31%, $p<0.01$), 70%DLCO% predicted (77±29 versus 131±39%, $p<0.001$), and (70%-R)DLCO% (4±8 versus 31±16%, $p<0.001$) than patients without pulmonary complications, indicating mild diffusing capacity impairment at rest and inadequate increase in DLCO during exercise.

COMPARISON OF THE VARIABLES USED FOR PREOPERATIVE EVALUATION

The analyses presented previously (Table V-VII) showed that, the four preoperative variables, that were best at discriminating between patients with and without complications, were (70%-R)DLCO%, DLCO% predicted, VO2max/kg, and FEV1% predicted. Among these variables, (70%-R)DLCO% was the best in discriminating between patients with and without overall complications, mortality, cardiovascular morbidity, and pulmonary morbidity. Although the four variables showed significant differences between patients with and without overall complications ($p<0.001$), only (70%-R)DLCO% was significantly different between patients with and without mortality ($p<0.01$). For cardiovascular morbidity, (70%-R)DLCO%, DLCO% predicted, and VO2max/kg were significantly different between patients with and without complications but there was no difference in FEV1% predicted. However all these four variables were significantly different between patients with and without pulmonary morbidity ($p<0.001$).

The boxplots [Mould, 1998] of these 4 variables for overall complications are shown in

Figure 7. The central tendency of patients without overall complications was different from that of patients with overall complications, and there was no extreme or outlying value in either group. For (70%-R)DLCO%, the smallest value of patients without overall complications was separated from the interquartile range of the patients with overall complications (large difference), and the distribution of the former was approximately symmetric while that of the latter was slightly positively skewed. For DLCO% predicted, the interquartile range of the former was separated from the interquartile range of the latter (moderate difference), while for VO2max/kg and FEV1% predicted, the interquartile range of the former slightly overlapped the interquartile range of the latter (small difference). The boxplot was not created for mortality because there were only 2 mortality cases. When the boxplots of these 4 variables for cardiovascular morbidity and pulmonary morbidity were created (Figure 8 and 9), the central tendency of the patients without both complications was different from that of the patients with both complications, and there was no extreme or outlying value in either group. The interquartile range of the former was separated from the interquartile range of the latter (moderate difference) in (70%-R)DLCO% and DLCO% predicted, while the interquartile range of the former slightly overlapped the interquartile range of the latter (small difference) in VO2max/kg and FEV1% predicted.

Logistic regression

Multiple variable analysis through stepwise logistic regression, showed that models combining different variables did not improve significantly the prediction of overall

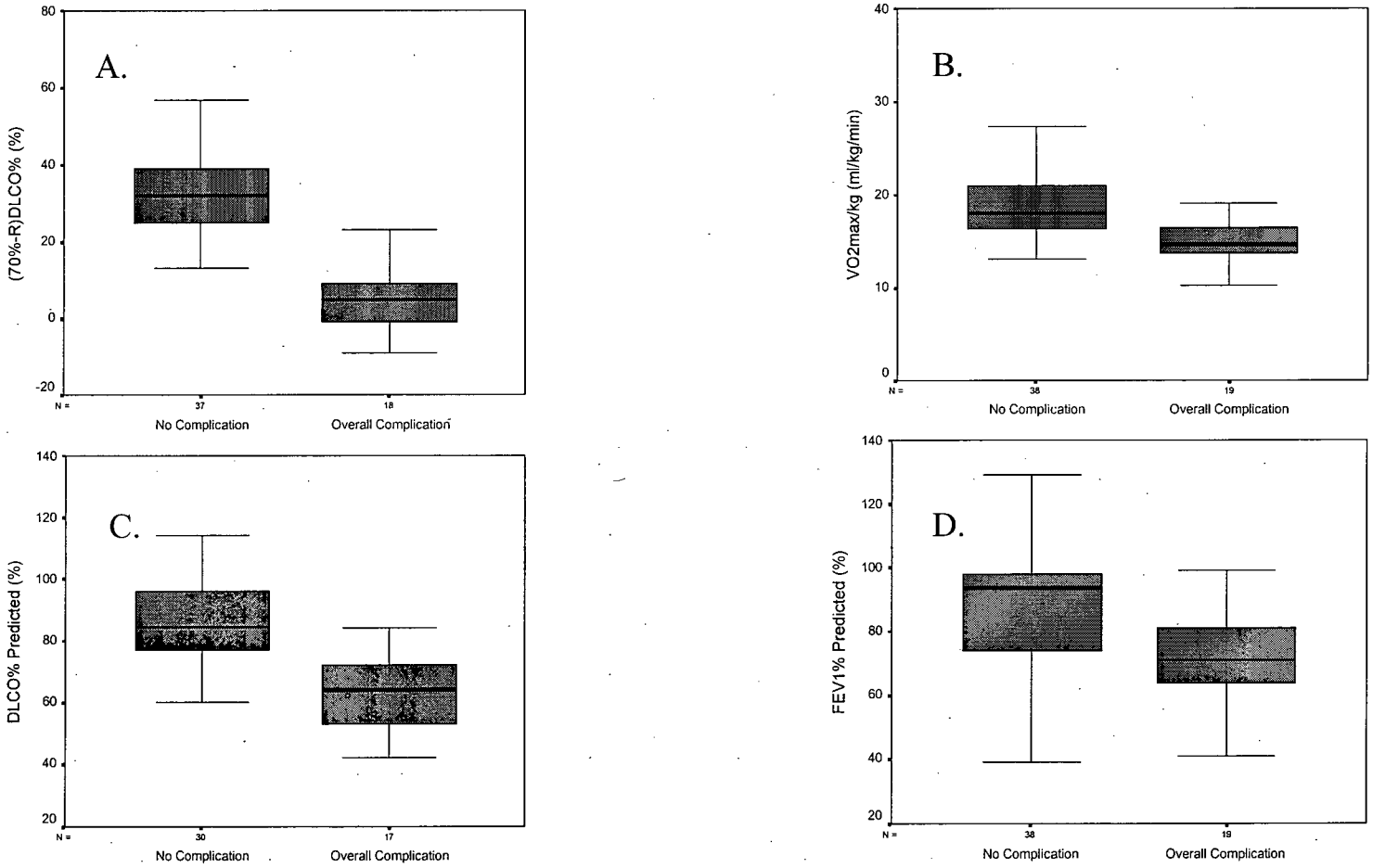

Figure 7. The boxplots of variables for overall complications. The central tendency of patients with complications was different from that of patients without complications for each variable, while the difference was the largest for (70%-R)DLCO% (A) and the smallest for VO2max/kg and FEV1% predicted (B and D).

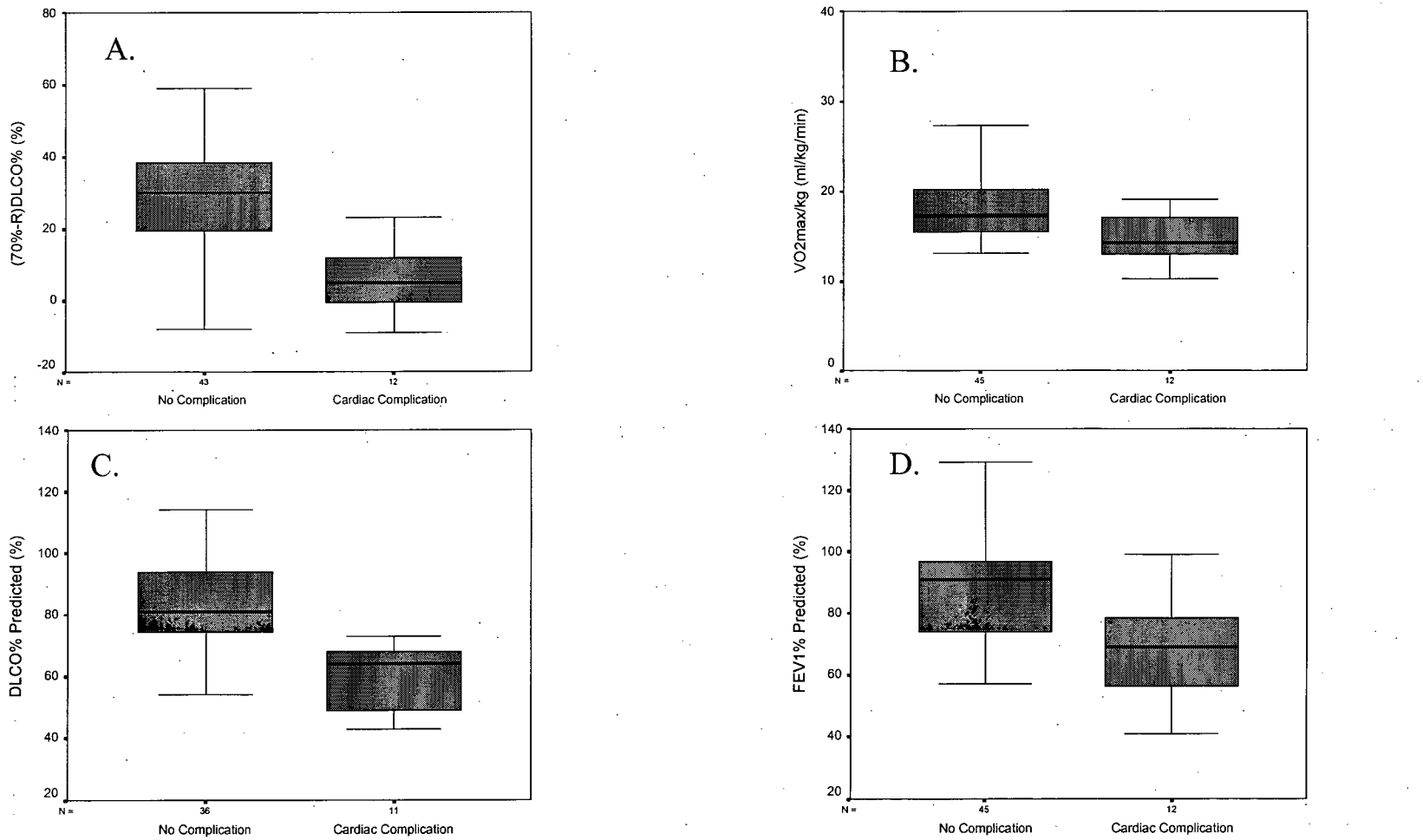

Figure 8. The boxplots of variables for cardiovascular complications. The central tendency of patients with complications was different from that of patients without complications for each variable, while the difference was the largest for (70%-R)DLCO% and DLCO% predicted (A and C), and the smallest for VO2max/kg and FEV1% predicted (B and D).

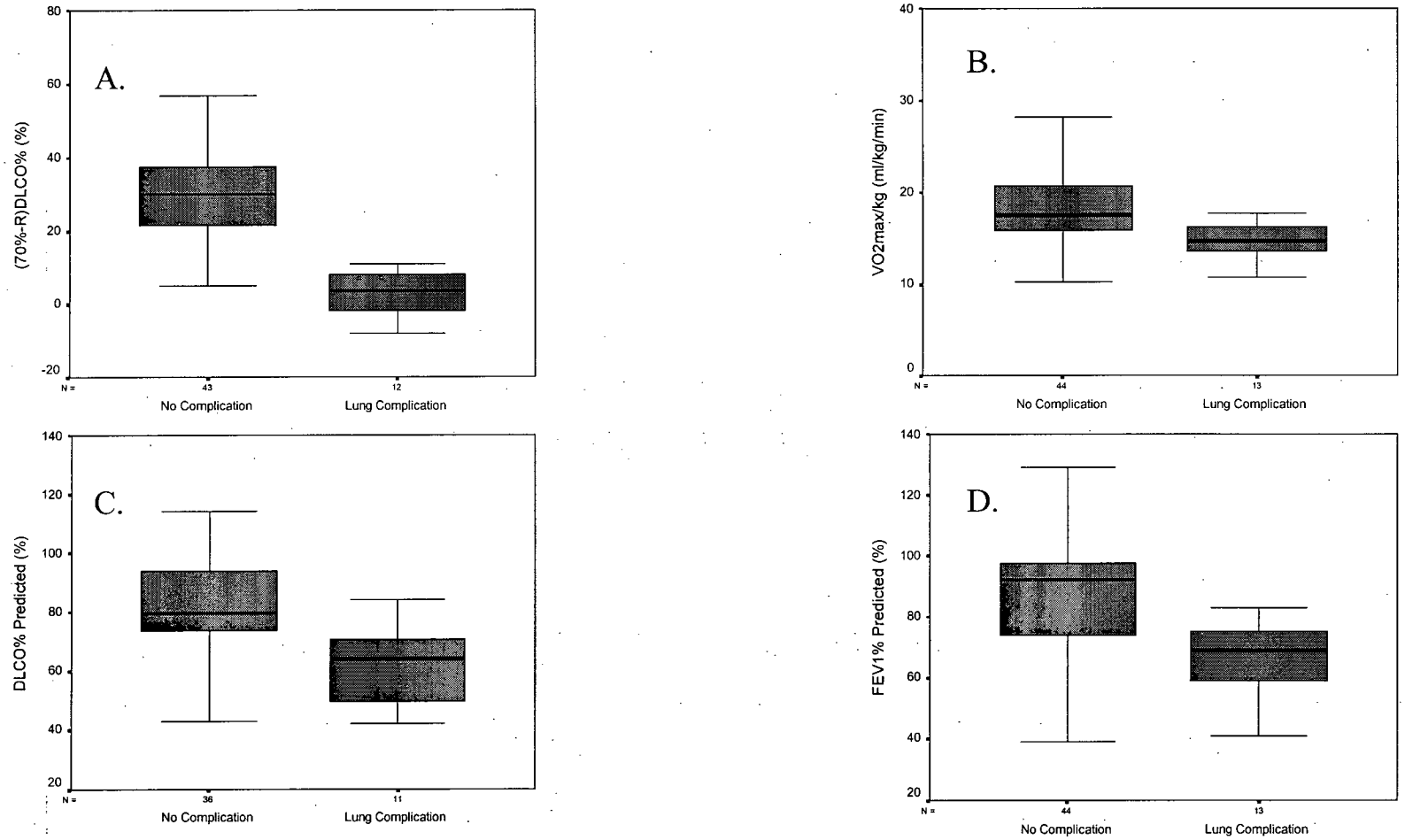

Figure 9. The boxplots of variables for pulmonary complications. The central tendency of patients with complications was different from that of patients without complications for each variable, while the difference was the largest for (70%-R)DLCO% and DLCO% predicted (A and C), and the smallest for VO2max/kg and FEV1% predicted (B and D).

complications, mortality, cardiovascular morbidity, and pulmonary morbidity as compared with the single variable analysis. Table VIII shows the prediction equations for the single variable analysis; it appears that the best predictor is (70%-R)DLCO% for overall complications ($p<0.001$), cardiovascular morbidity ($p<0.001$), and pulmonary morbidity ($p<0.001$). For mortality, the best predictor appears to be (70%-R)DLCO%, but owing to the small number of cases, the prediction equation does not reach statistical significance ($p=0.079$)(Table VIII). The incidence of overall complications, cardiac morbidity, pulmonary morbidity, and mortality was calculated for the 6 intervals (≥25, 25 to 20, 20 to 15, 15 to 10, 10 to 5, and <5%) for (70%-R)DLCO%, the best predictive preoperative variable (Figure 10). There was a marked increase in overall complications for (70%-R)DLCO% <10% (Figure 10), while the two mortality cases both had (70%-R)DLCO% <5%.

ROC curve

To evaluate what level of preoperative variables correlated with complications, the incidence of complications was calculated for 6 intervals as follows: (≥25, <25, <20, <15, <10, and <5%) for (70%-R)DLCO%, (≥24, <24, <21, <18, <15, and <12 ml/kg/min) for VO2max/kg, (≥90, <90, <80, <70, <60, and <50%) for DLCO% predicted and FEV1% predicted. The ROC curves of these four variables for overall complications, mortality, cardiovascular morbidity, and pulmonary morbidity were determined, and AURC values were calculated (Table IX). The largest AURC was 0.97 (Table IX) calculated from the ROC curve of (70%-R)DLCO% for overall complications (Figure 11), and this again indicated that (70%-R)DLCO% was the best

Table VIII. Prediction equations of postoperative complications by preoperative variables

Complications	Predicted equations	p value
(70%-R)DLCO%:		
Overall complications	ln (P/1-P)=4.105-0.271*(70%-R)DLCO%	<0.001
Cardiovascular complications	ln (P/1-P)=0.703-0.118*(70%-R)DLCO%	<0.001
Pulmonary complications	ln (P/1-P)=1.280-0.171*(70%-R)DLCO%	<0.001
Mortality	ln (P/1-P)=-1.899-0.146*(70%-R)DLCO%	0.079 (NS)
(70%-R)DLCO/VO2:		
Overall complications	ln (P/1-P)=3.219-0.802*(70%-R)DLCO/VO2	<0.001
Cardiovascular complications	ln (P/1-P)=0.679-0.425*(70%-R)DLCO/VO2	<0.01
Pulmonary complications	ln (P/1-P)=0.954-0.511*(70%-R)DLCOVO2	<0.01
Mortality	ln (P/1-P)=-1.988-0.632*(70%-R)DLCO/VO2	0.085 (NS)
(70%-R)DLCO/VO2%:		
Overall complications	ln (P/1-P)=2.919-9.262*(70%-R)DLCO/VO2%	<0.001
Cardiovascular complications	ln (P/1-P)=0.577-5.019*(70%-R)DLCO/VO2%	<0.01
Pulmonary complications	ln (P/1-P)=0.916-6.367*(70%-R)DLCO/VO2%	<0.01
Mortality	ln (P/1-P)=-2.047-7.934*(70%-R)DLCO/VO2%	0.081 (NS)

P: the probability of developing complication; NS: not significant.

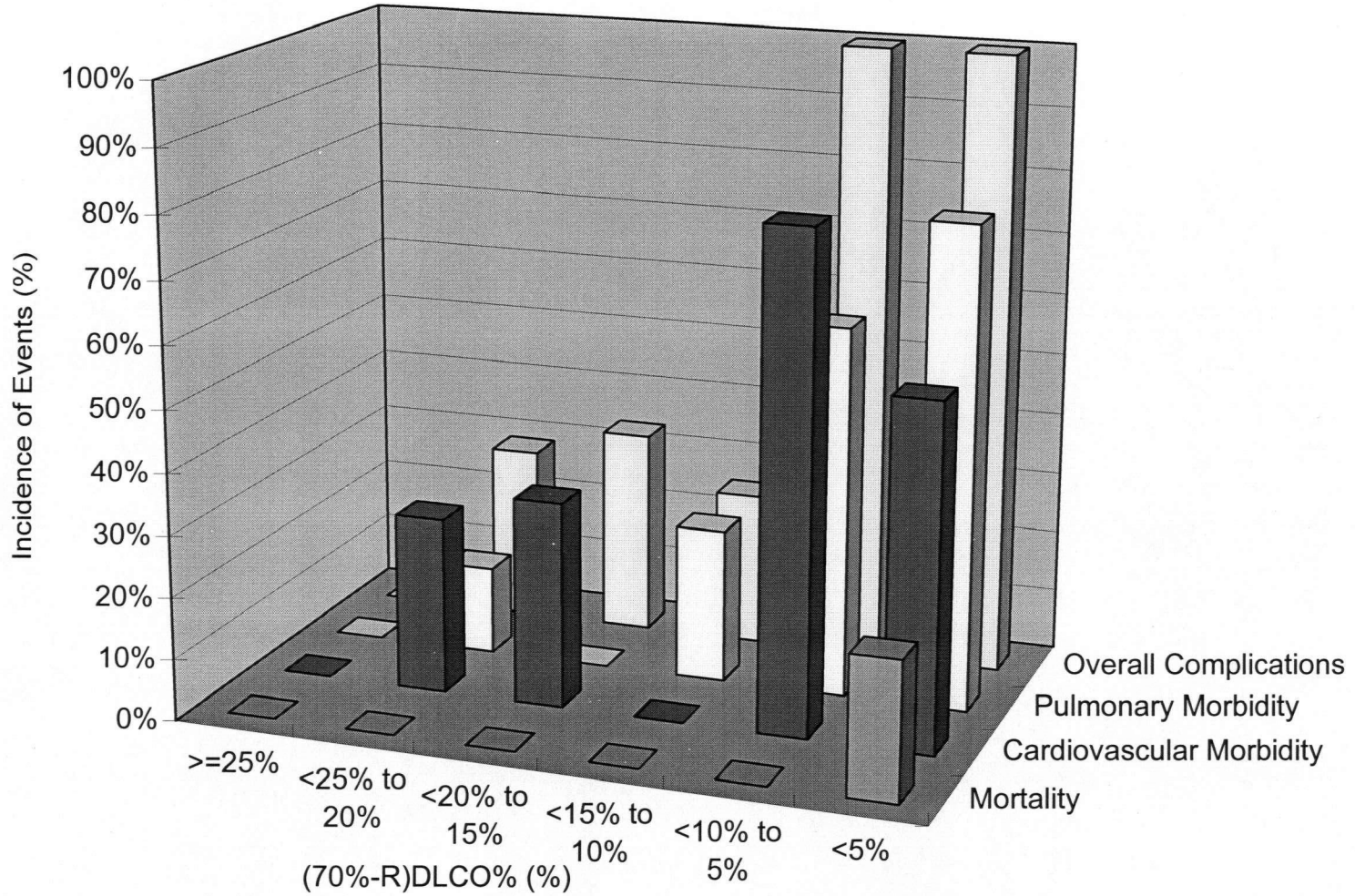

Figure 10. Incidence of mortality, cardiovascular morbidity, pulmonary morbidity, and overall complications in relation to (70%-R)DLCO%. There was a marked increase in overall complications for (70%-R)DLCO% < 10%.

Table IX. The area under receiver operating characteristic curve of preoperative variables for postoperative complications

Variables	Complications	AURC
(70%-R)DLCO%	Overall complications	0.97
	Cardiovascular morbidity	0.92
	Pulmonary morbidity	0.93
	Mortality	0.88
VO2max/kg	Overall complications	0.86
	Cardiovascular morbidity	0.78
	Pulmonary morbidity	0.82
	Mortality	0.68
DLCO% predicted	Overall complications	0.90
	Cardiovascular morbidity	0.88
	Pulmonary morbidity	0.88
	Mortality	0.70
FEV1% predicted	Overall complications	0.77
	Cardiovascular morbidity	0.63
	Pulmonary morbidity	0.80
	Mortality	0.60
(70%-R)DLCO/VO2	Overall complications	0.95
	Cardiovascular morbidity	0.92
	Pulmonary morbidity	0.92
	Mortality	0.86
(70%-R)DLCO/VO2%	Overall complications	0.94
	Cardiovascular morbidity	0.91
	Pulmonary morbidity	0.91
	Mortality	0.86

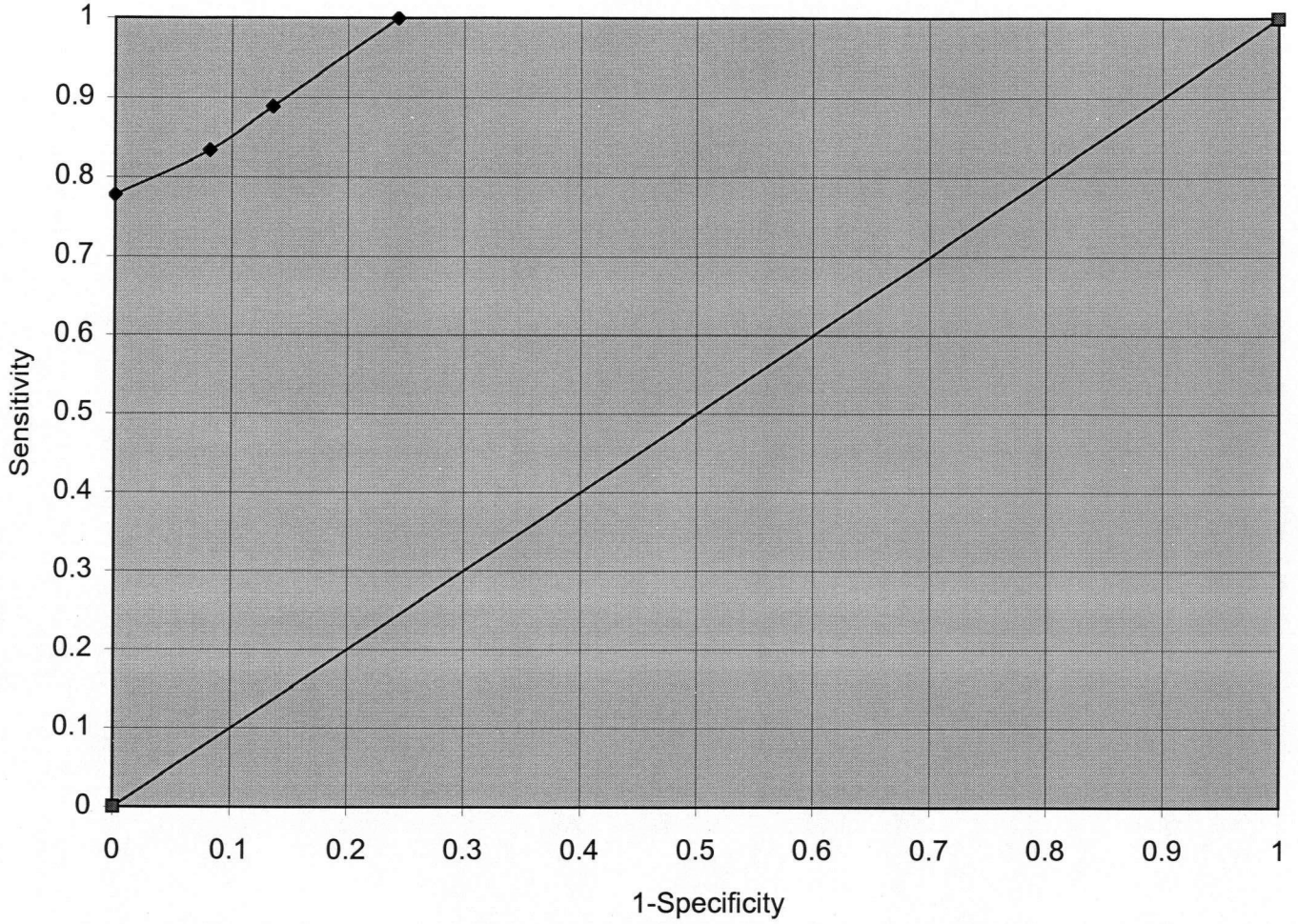

Figure 11. The ROC curve of (70%-R)DLCO% for prediction of overall complications. The solid line is the line of identity for a test without any discrimination. The AURC was 0.97 and the best cut-off limit was 10% with sensitivity 78% and specificity 100%.

predictor of complications.

The best cut-off limit was defined by the point closest to the left-upper corner, and was 10% in the ROC curve of (70%-R)DLCO% for overall complications with sensitivity 78% and specificity 100% ($p<0.001$)(Figure 11). Fourteen of 18 patients with overall complications had a (70%-R)DLCO% <10% (sensitivity = 78%), and 37 of 37 patients without complications were above or equal this limit (specificity = 100%). This gave a relative risk of 10, and a risk difference of 90% ($p < 0.001$, Fisher's exact test). For VO2max/kg (Figure 12), a level of 15ml/kg/min gave the best cut-off limit; 11 of the 19 patients with overall complications had a VO2max/kg < 15ml/kg/min (sensitivity = 58%), and 34 of 38 patients without complications were above or equal this limit (specificity = 89%). This resulted in a relative risk of 4, a risk difference of 54%, and odds ratio of 12 ($p < 0.001$, Fisher's exact test). For DLCO% (Figure 13), a level of 70% was the best cut-off limit; 12 of 17 patients with overall complications had a DLCO% < 70% (sensitivity = 71%), and 28 of 30 patients without complications were above or equal this limit (specificity = 93%). This gave a relative risk of 6, a risk difference of 71%, and odds ratio of 34 ($p < 0.001$, Fisher's exact test). For FEV1% (Figure 14), a level of 80% gave the best cut-off limit; 13 of the 19 patients with overall complications had a FEV1% < 80% (sensitivity = 68%), and 26 of 38 patients without overall complication were above or equal this limit (specificity = 68%). This resulted in a relative risk of 3, a risk difference of 33%, and odds ratio of 5 ($p < 0.05$, Fisher's exact test). Furthermore, postoperative complications were compared by these cut-off limits for these preoperative lung function variables in Table X. Of all the variables, the only predictor of mortality was again (70%-R)DLCO%. The two variables

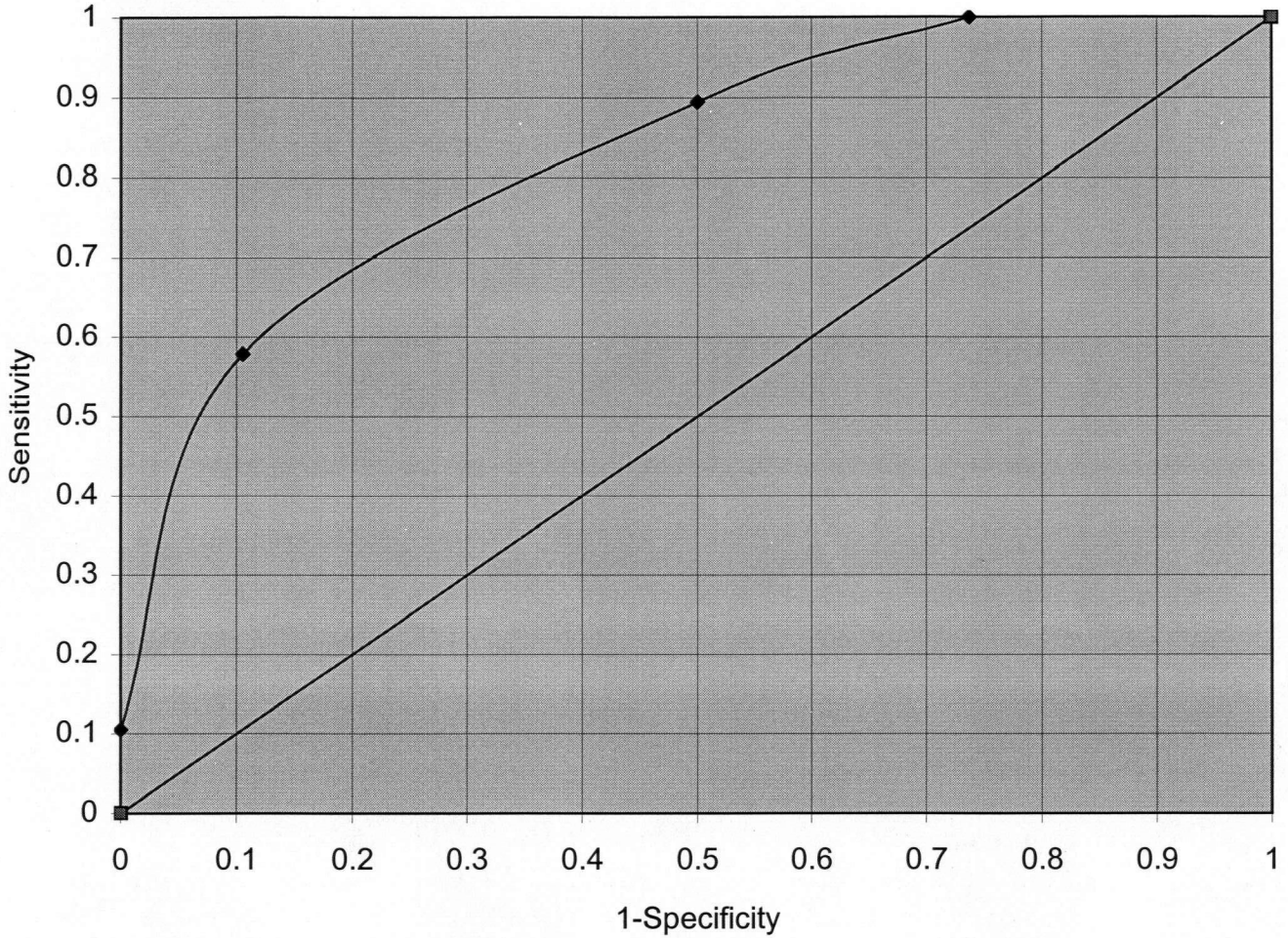

Figure 12. The ROC curve of VO2max/kg for prediction of overall complications. The solid line is the line of identity for a test without any discrimination. The AURC was 0.86; the best cut point was 15 ml/kg/min with sensitivity 58% and specificity 89%.

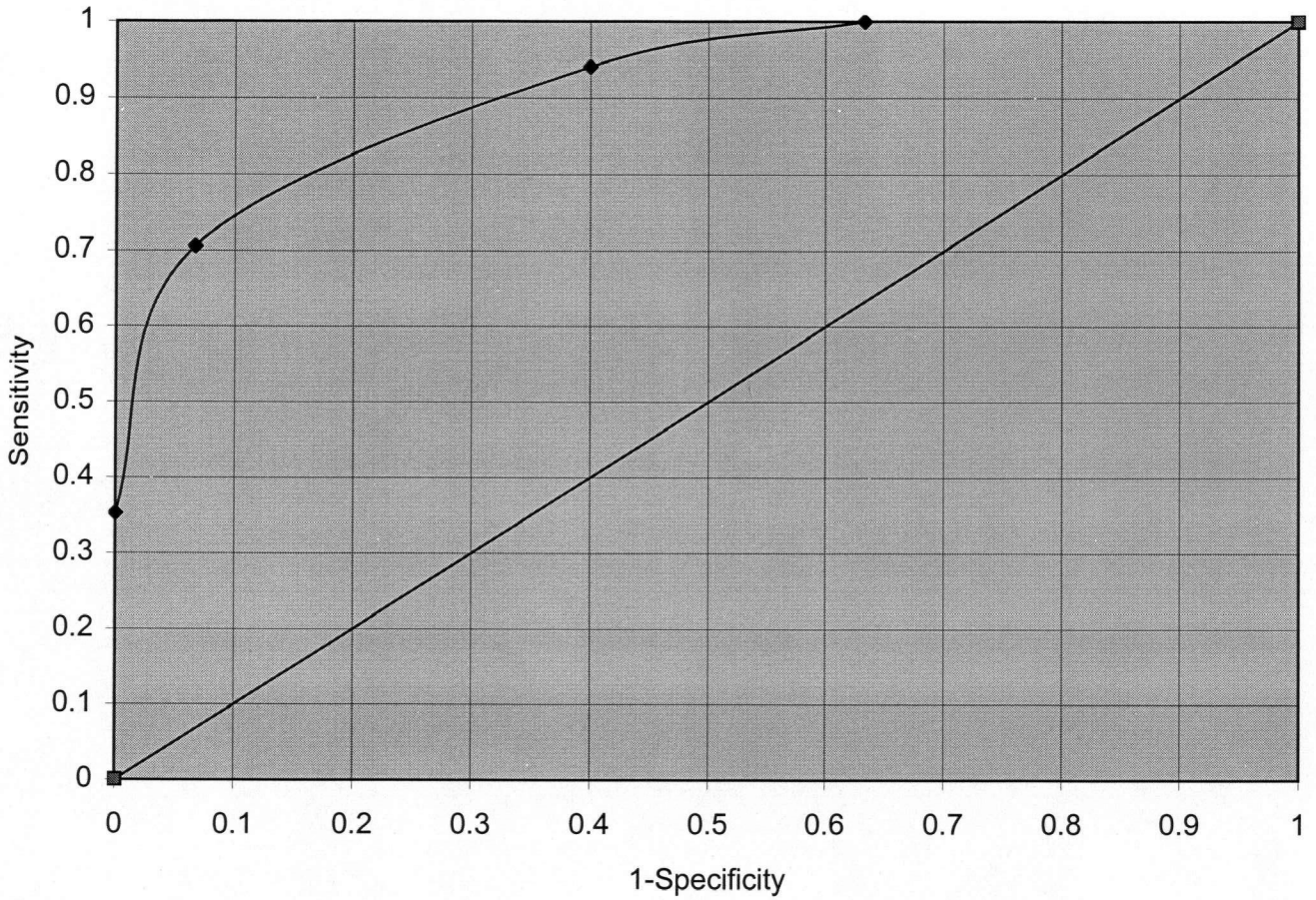

Figure 13. The ROC curve of DLCO% predicted for prediction of overall complications. The solid line is the line of identity for a test without any discrimination. The AURC was 0.90; the best cut point was 70% with sensitivity 71% and specificity 93%.

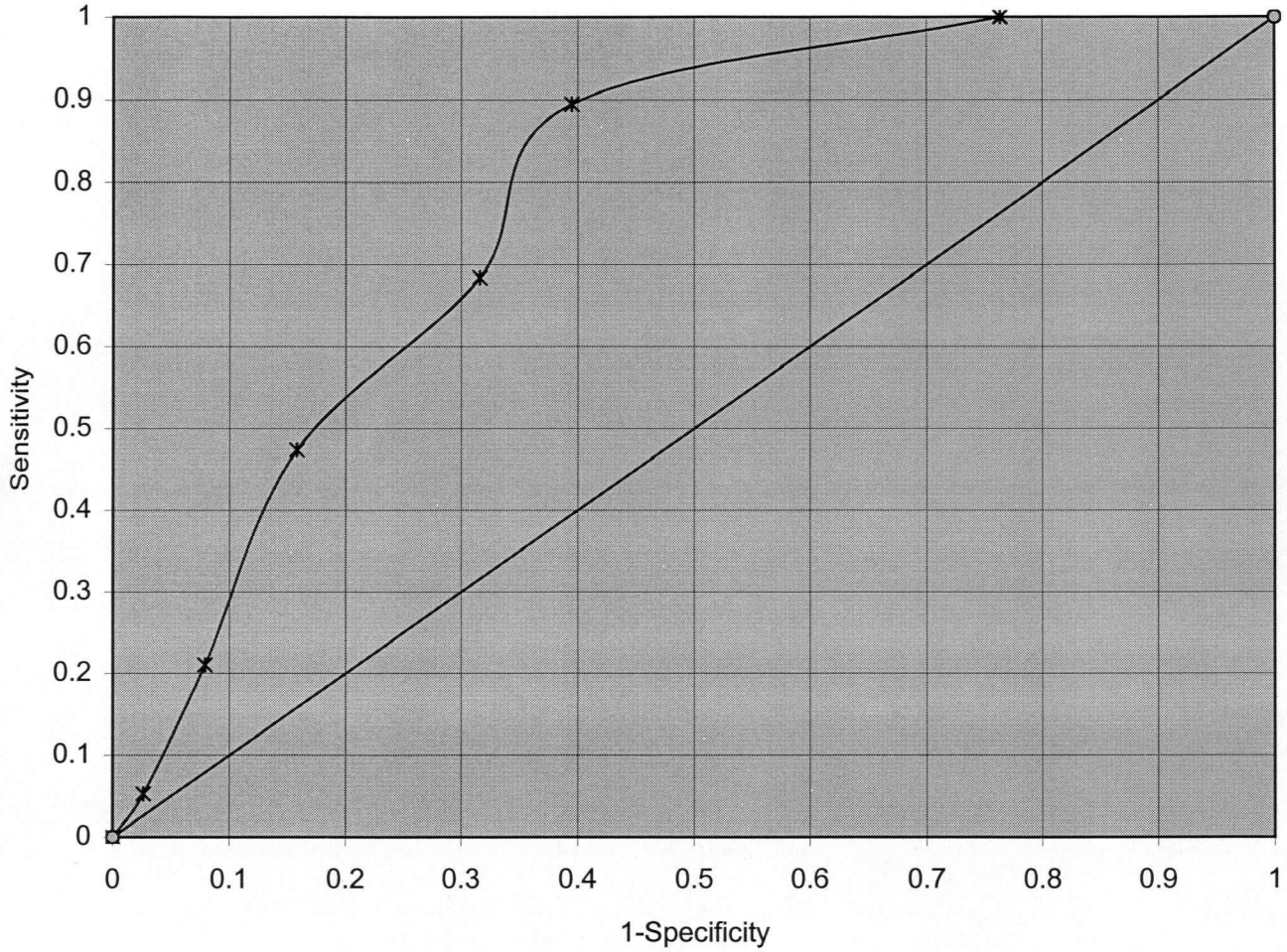

Figure 14. The ROC curve of FEV1% predicted for prediction of overall complications. The solid line is the line of identity for a test without any discrimination. The AURC was 0.77; the best cut point was 80% with sensitivity 68% and specificity 68%.

Table X. Comparison of postoperative complications using cut-off limits of preoperative variables

(70%-R)DLCO% (%)	<X	≥X	p value
Overall complications (X=10)	100%(14/14)	10%(4/41)	<0.001
Cardiovascular morbidity (X=10)	64%(9/14)	7%(3/41)	<0.001
Pulmonary morbidity (X=15)	61%(11/18)	3%(1/37)	<0.001
Mortality (X=5)	22%(2/9)	0%(0/46)	<0.05
VO2max/kg (ml/kg/min)	<X	≥X	p value
Overall complications (X=15)	73%(11/15)	19%(8/42)	<0.001
Cardiovascular morbidity (X=21)	40%(19/47)	0%(0/10)	<0.05
Pulmonary morbidity (X=18)	36%(13/36)	0%(0/21)	<0.01
Mortality (X=15)	7%(1/15)	2%(1/42)	NS
DLCO% predicted	<X	≥X	p value
Overall complications (X=70)	86%(12/14)	15%(5/33)	<0.001
Cardiovascular morbidity (X=70)	64%(9/14)	6%(2/33)	<0.001
Pulmonary morbidity (X=70)	57%(8/14)	9%(3/33)	<0.001
Mortality (X=70)	7%(1/14)	0%(0/33)	NS
FEV1% predicted	<X	≥X	p value
Overall complications (X=80)	52%(13/25)	19%(6/32)	<0.05
Cardiovascular morbidity (X=70)	27%(4/15)	19%(8/42)	NS
Pulmonary morbidity (X=70)	53%(8/15)	26%(11/42)	<0.01
Mortality (X=60)	14%(1/7)	2%(1/50)	NS
(70%-R)DLCO/VO2 (*)	<X	≥X	p value
Overall complications (X=4)	83%(15/18)	8%(3/37)	<0.001
Cardiovascular morbidity (X=4)	56%(10/18)	5%(2/37)	<0.001
Pulmonary morbidity (X=2)	90%(9/10)	7%(3/45)	<0.001
Mortality (X=2)	20%(2/10)	0%(0/45)	<0.05
(70%-R)DLCO/VO2%	<X	≥X	p value
Overall complications (X=0.2)	100%(12/12)	14%(6/43)	<0.001
Cardiovascular morbidity (X=0.2)	75%(9/12)	7%(3/43)	<0.001
Pulmonary morbidity (X=0.2)	75%(9/12)	7%(3/43)	<0.001
Mortality (X=0.2)	17%(2/12)	0%(0/43)	<0.05

NS: not significant; *: (ml/min/mmHg)/(L/min).

VO2max/kg and DLCO% predicted did predict overall complications, cardiac morbidity, and pulmonary morbidity, but not mortality, while FEV1% predicted did predict overall complications, and pulmonary morbidity, but not cardiac morbidity or mortality. Thus, the best variable at predicting complications was again (70%-R)DLCO%.

Because there were 13 cases who had segmentectomy, wedge resection, or only thoracotomy without resection, and did not have any complications, we repeated analysis of the clinical evaluation, lung function variables, and exercise data (shown in Table V-VII) in the 44 patients who had lobectomy, bilobectomy, or pneumonectomy. The results (Appendix VIII) were similar to the results for all 57 cases. Furthermore, logistic regression analysis excluding these 13 cases (Appendix IX-A), was similar to the results for all 57 cases (Appendix IX-B).

FURTHER ANALYSIS OF THE INCREASE IN 3EQ-DLCO DURING EXERCISE

Since the increase in DLCO with exercise is dependent on the level of exercise, the increase in 3EQ-DLCO in each subject, from rest to steady state exercise at 70% of maximal workload, was expressed as a ratio of the increase in VO2 from rest to that level of exercise ((70%-R)DLCO/VO2); mean data for all subjects are shown in Table III. Patients with complications did not increase 3EQ-DLCO to the same extent as the patients without complications (1.7 ± 2.7 versus 9.4 ± 4.1 (ml/min/mmHg)/(L/min), $p<0.001$) for a given increase in VO2 (Table VII). Mean data of 3EQ-DLCO at rest and during steady state exercise at the higher workload are plotted against VO2 in Figure 15; patients with complications had only a minimal increase in 3EQ-DLCO with increasing VO2, as compared with patients without complications. To adjust for individual differences in 3EQ-DLCO and in VO2 due to age, sex, and height, the same data was calculated expressing the increase in 3EQ-DLCO as % of predicted resting SB-DLCO and VO2 as % of predicted maximal VO2 ((70%-R)DLCO/VO2%). Mean data for all subjects are shown in Table III, and data for patients with and without complications are compared in Table VII and Figure 16. Again, patients with complications did not increase 3EQ-DLCO% predicted to the same extent as patients without complications (0.13 ± 0.23 versus

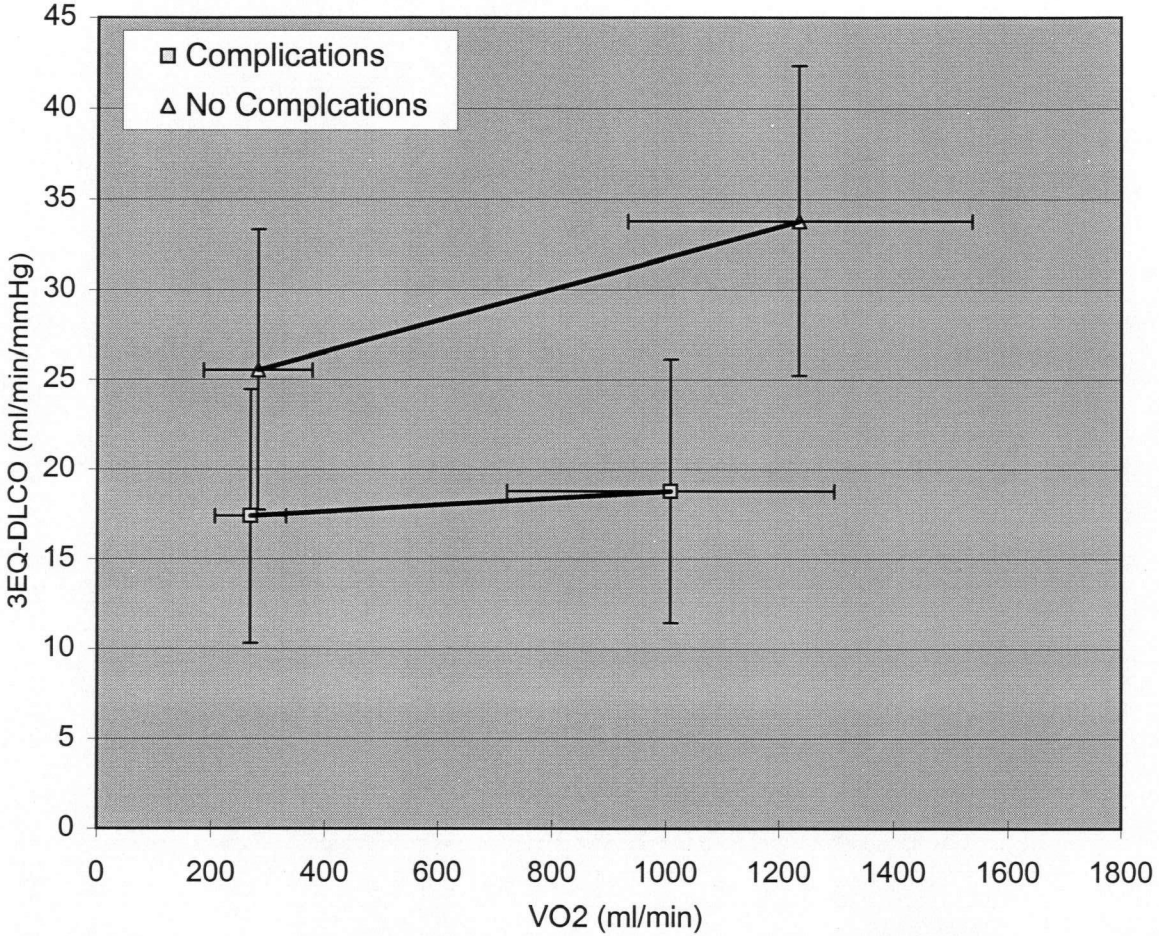

Figure 15. Mean 3EQ-DLCO versus mean VO2 at rest and during the higher level of steady state exercise (bars indicate SD). Patients with complications had a lower increase in DLCO with exercise than patients without complications.

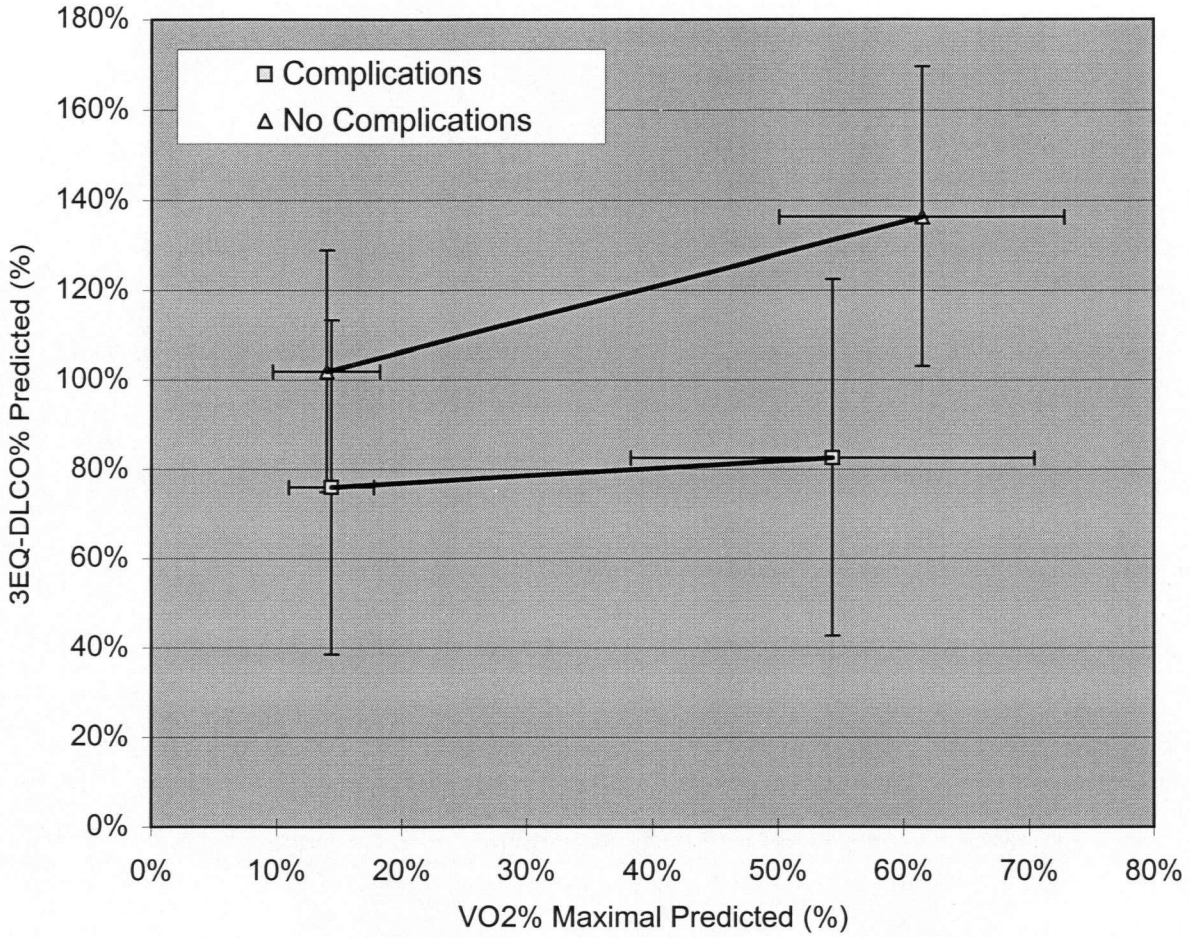

Figure 16. Mean 3EQ-DLCO% predicted versus mean VO2% maximal predicted at rest and during steady state exercise (bars indicate SD). Patients with complications had a lower increase in DLCO with exercise than patients without complications.

0.76±0.36, $p<0.001$) for a given increase in VO2.

The boxplots of (70%-R)DLCO/VO2 and (70%-R)DLCO/VO2% for overall complications (Figure 17) indicated that, the central tendency of patients without complications was different from that of patients with complications, and there was no extreme or outlying value in either group. The interquartile range of the former was separated from the interquartile range of the latter (moderate difference); the distribution of the former was slightly negatively skewed and that of the latter was slightly positively skewed. Therefore, the differences between the distribution of both variables for patients without overall complications and patients with overall complications were less than that of (70%-R)DLCO% (Figure 7). The boxplots of each variable for cardiovascular morbidity and pulmonary morbidity (Figure 18 and 19) showed that, the central tendency of patients without complications was different from that of patients with complications for each variables, and there was no extreme or outlying value in either group. The interquartile range of the former was separated from the interquartile range of the latter (moderate difference) for each variable; therefore, the differences between the distribution of each variable for patients without complications and patients with complications were similar to that of (70%-R)DLCO% (figure 8-9).

The discriminatory roles of (70%-R)DLCO/VO2 and (70%-R)DLCO/VO2% in preoperative evaluation were similar to (70%-R)DLCO%, and better than the other three preoperative variables (DLCO% predicted, VO2max/kg, and FEV1% predicted) in all aspects (Table VII). Either of them was very significantly different between patients with and without

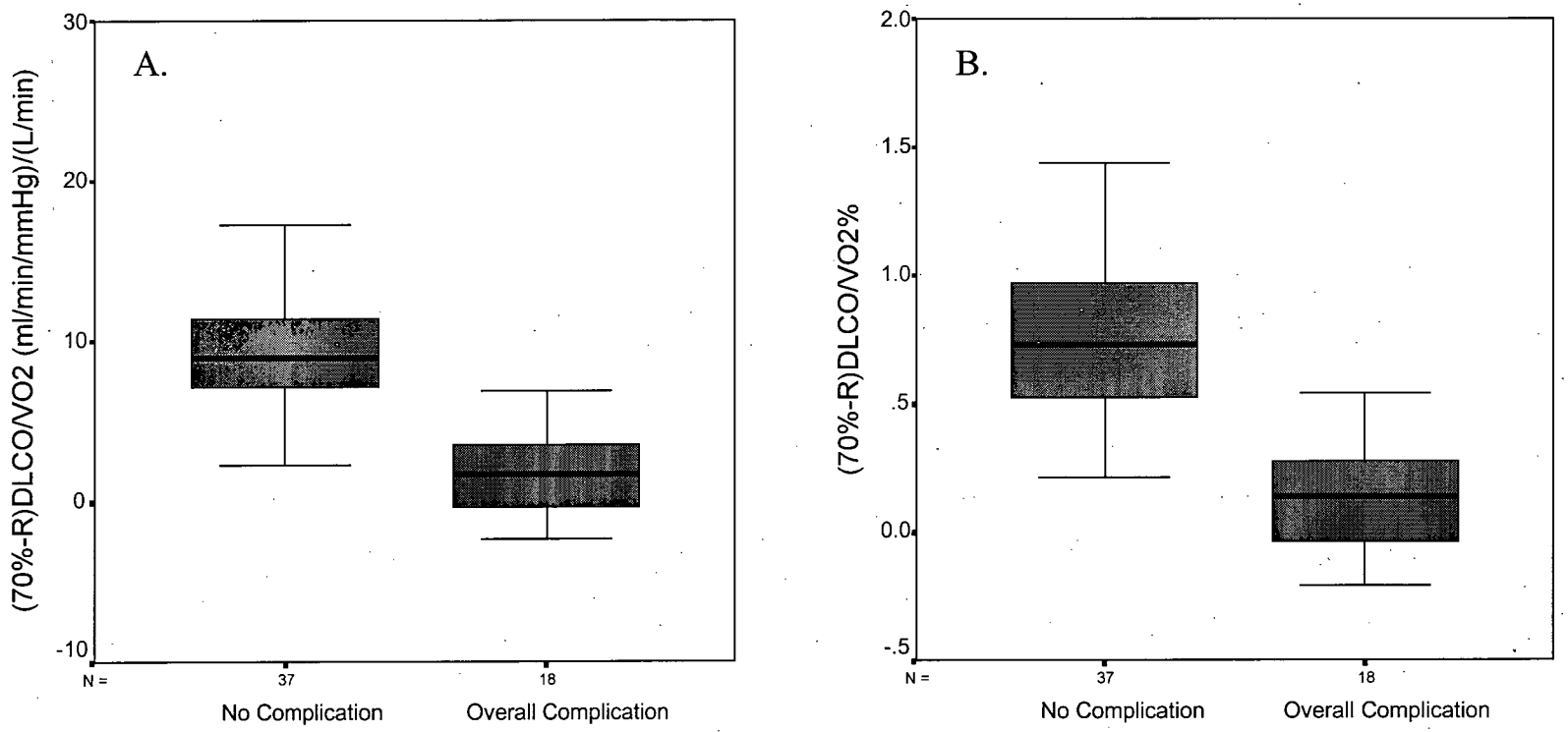

Figure 17. The boxplots of (70%-R)DLCO/VO2 and (70%-R)DLCO/VO2% for overall complications. The central tendency of patients with complications was different from that of patients without complications for each variable, while the difference was moderate and similar to that of DLCO% predicted for overall complications (Figure 6C).

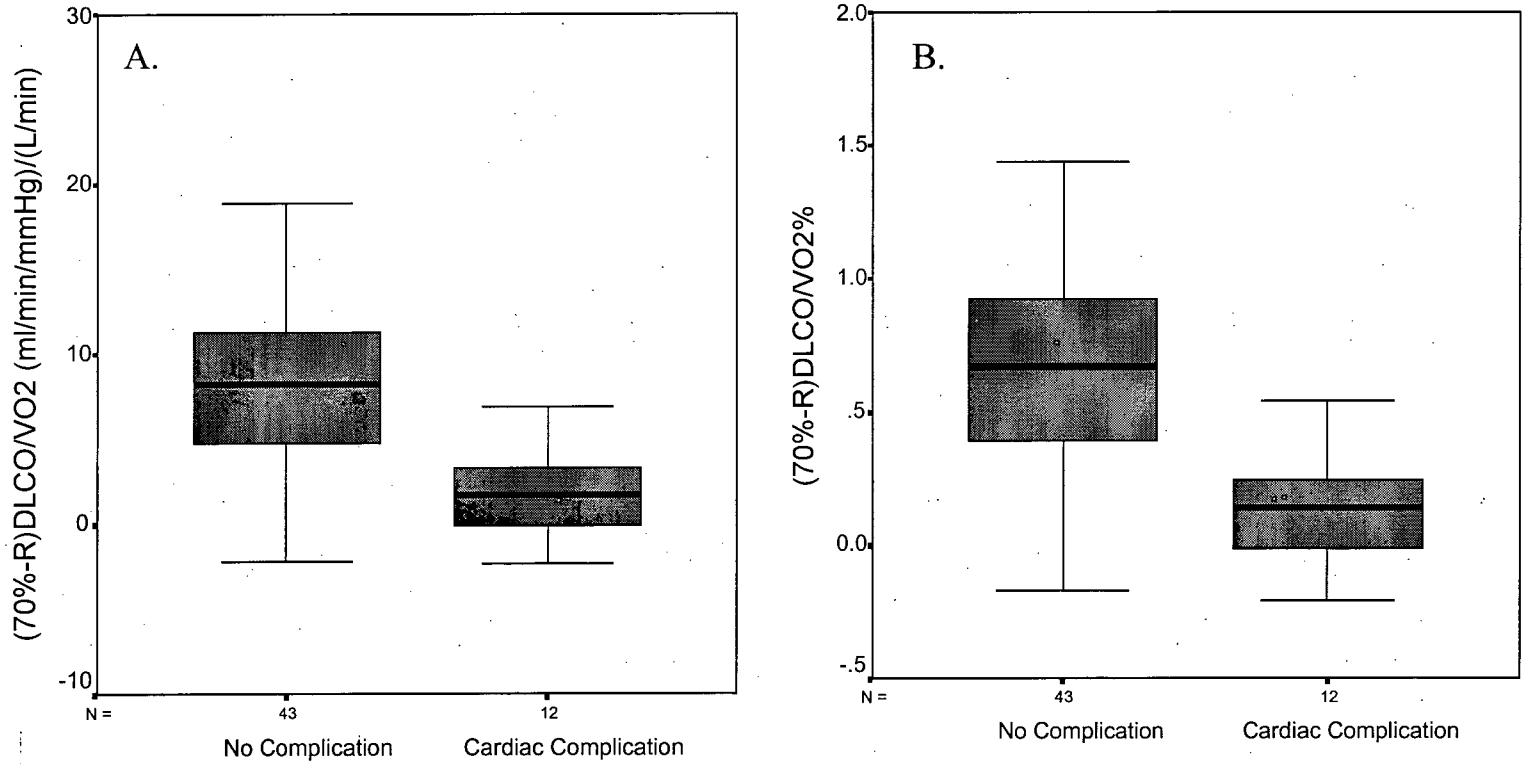

Figure 18. The boxplots of (70%-R)DLCO/VO2 and (70%-R)DLCO/VO2% for cardiovascular complications. The central tendency of patients with complications was different from that of patients without complications for each variable, while the difference was moderate and similar to those of (70%-R)DLCO% and DLCO% predicted for cardiovascular complications (Figure 7A and 7C).

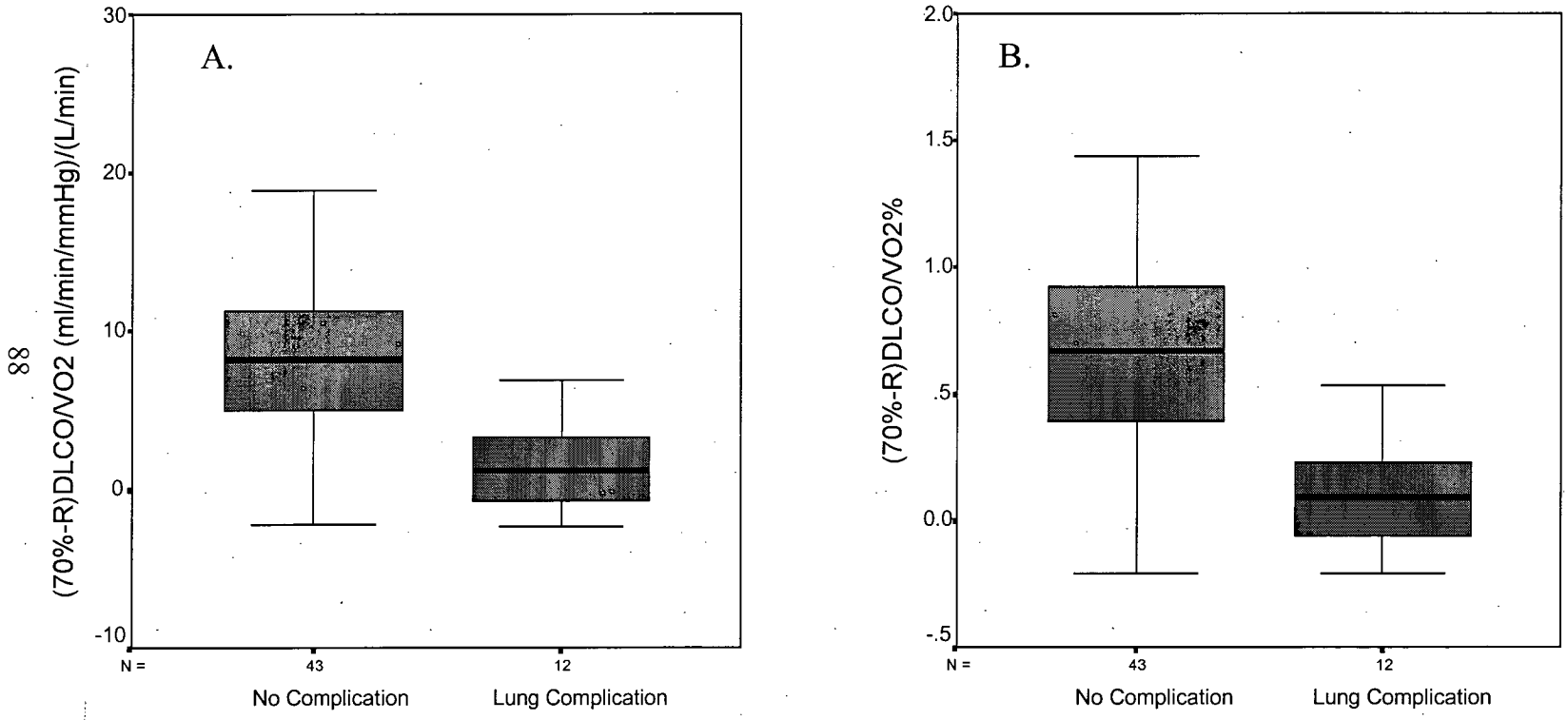

Figure 19. The boxplots of (70%-R)DLCO/VO2 and (70%-R)DLCO/VO2% for pulmonary complications. The central tendency of patients with complications was different from that of patients without complications for each variable, while the difference was moderate and similar to those of (70%-R)DLCO% and DLCO% predicted for pulmonary complications (Figure 8A and 8C).

overall complications (Table VII), cardiovascular morbidity and pulmonary morbidity ($p<0.001$), but just fairly significantly different between patients with and without mortality ($p<0.05$). Using multiple variable analysis through stepwise logistic regression, no model was found that after combining different variables improved significantly the prediction of overall complications, mortality, cardiovascular morbidity, and pulmonary morbidity as compared with the single variable analysis. These two variables were similar to (70%-R)DLCO% and better than the other three preoperative variables in predicting overall complications ($p<0.001$, $r=-0.732$ for (70%-R)DLCO/VO2; $p<0.001$, $r=-0.726$ for (70%-R)DLCO/VO2%), cardiovascular morbidity ($p<0.001$, $r=-0.555$ for (70%-R)DLCO/VO2; $p<0.001$, $r=-0.549$ for (70%-R)DLCO/VO2%), and pulmonary morbidity ($p<0.001$, $r=-0.591$ for (70%-R)DLCO/VO2; $p<0.001$, $r=-0.588$ for (70%-R)DLCO/VO2%)(Table VIII). Each variable was similar to (70%-R)DLCO% in predicting mortality (Table VIII), but the predicted equation did not reach statistical significance due to the small number of cases ($p=0.085$, $r=-0.300$ for (70%-R)DLCO/VO2; $p=0.081$, $r=-0.297$ for (70%-R)DLCO/VO2%). The incidence of overall complications, cardiac morbidity, pulmonary morbidity, and mortality were calculated for 6 intervals (≥ 8, 8 to 6, 6 to 4, 4 to 2, 2 to 0, and <0) for (70%-R)DLCO/VO2 (Figure 20), and (≥ 0.8, 0.8 to 0.6, 0.6 to 0.4, 0.4 to 0.2, 0.2 to 0, and <0) for (70%-R)DLCO/VO2% (Figure 21). There were increased overall complications for (70%-R)DLCO/VO2 <4 and for (70%-R)DLCO/VO2% <0.2 (Figure 20 and 21), while the two mortality cases both had (70%-R)DLCO/VO2 <2 and (70%-R)DLCO/VO2% <0.2.

To evaluate what level of preoperative variables correlated with complications, the incidence of complications was calculated for 6 intervals (≥ 8, <8, <6, <4, <2, and <0) for (70%-

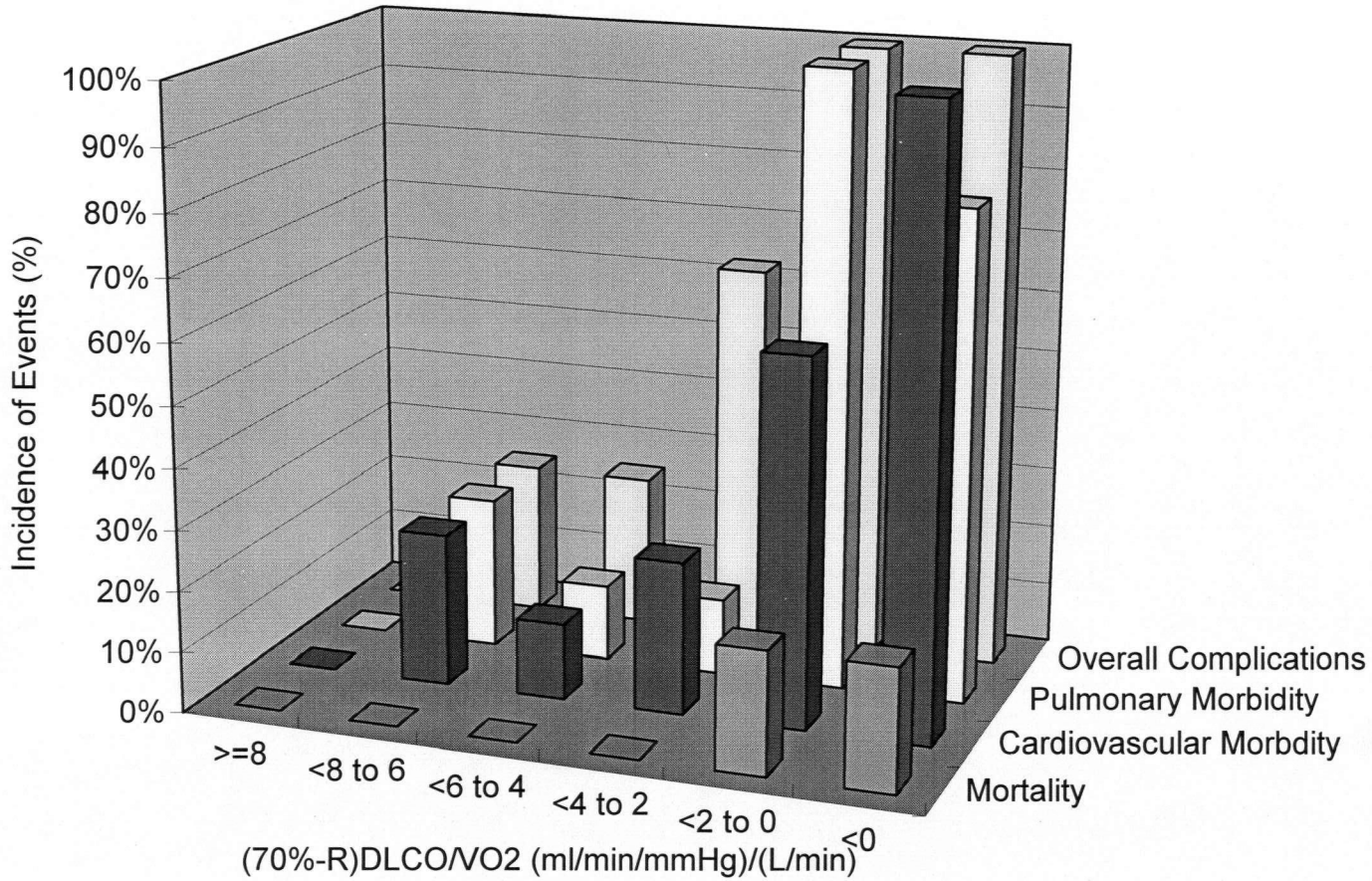

Figure 20. Incidence of mortality, cardiovascular morbidity, pulmonary morbidity, and overall complications in relation to (70%-R)DLCO/VO2. There was a marked increase in overall complications for (70%-R)DLCO/VO2 < 4 (ml/min/mmHg)/(L/min).

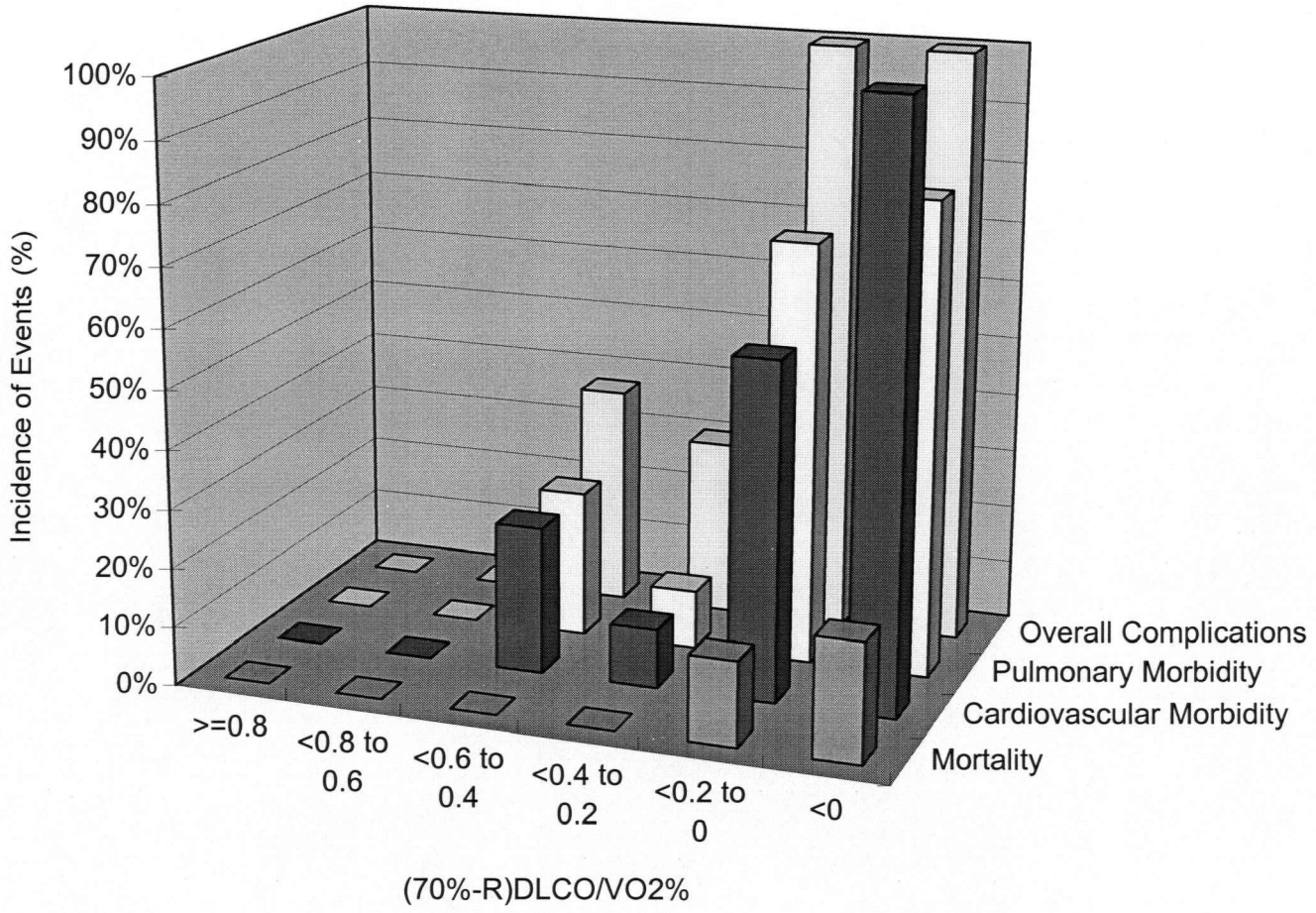

Figure 21. Incidence of mortality, cardiovascular morbidity, pulmonary morbidity, and overall complications in relation to (70%-R)DLCO/VO2%. There was a marked increase in overall complications for (70%-R)DLCO/VO2% < 0.2.

R)DLCO/VO2, and (≥0.8, <0.8, <0.6, <0.4, <0.2, and <0) for (70%-R)DLCO/VO2%.The ROC curve for each variable for overall complications, mortality, cardiovascular morbidity, and pulmonary morbidity were determined and the AURC values were calculated (Table IX). When compared with other three preoperative variables (VO2max/kg, DLCO% predicted, and FEV1% predicted) for overall complications, the AURC was 0.95 for (70%-R)DLCO/VO2, and the AURC was 0.94 for (70%-R)DLCO/VO2%. This indicated that either of them was better than the other three variables in predicting complications and similar to (70%-R)DLCO%. The ROC curve of (70%-R)DLCO/VO2 for overall complications is shown in Figure 22; the best cut-off limit was defined by the point closest to the left-upper corner and was 4 with sensitivity 83% and specificity 92% ($p<0.001$). Figure 23 shows that the best cut-off limit was 0.2 for the ROC curve of (70%-R)DLCO/VO2% for overall complications, with sensitivity 67% and specificity 100% ($p<0.001$). Postoperative complications by these cut-off limits for both variables were compared with the other variables in Table X. Again, each variable was similar to (70%-R)DLCO% in predicting mortality, which was not predicted by the other three variables. Therefore, (70%-R)DLCO% was as good or better than either (70%-R)DLCO/VO2 or (70%-R)DLCO/VO2% in predicting complications and was better than the other three preoperative variables (DLCO% predicted, VO2max/kg, and FEV1% predicted) in predicting complications including mortality. Moreover, (70%-R)DLCO% was simpler to obtain than either (70%-R)DLCO/VO2 or (70%-R)DLCO/VO2%, since it did not require measurement of VO2 during exercise.

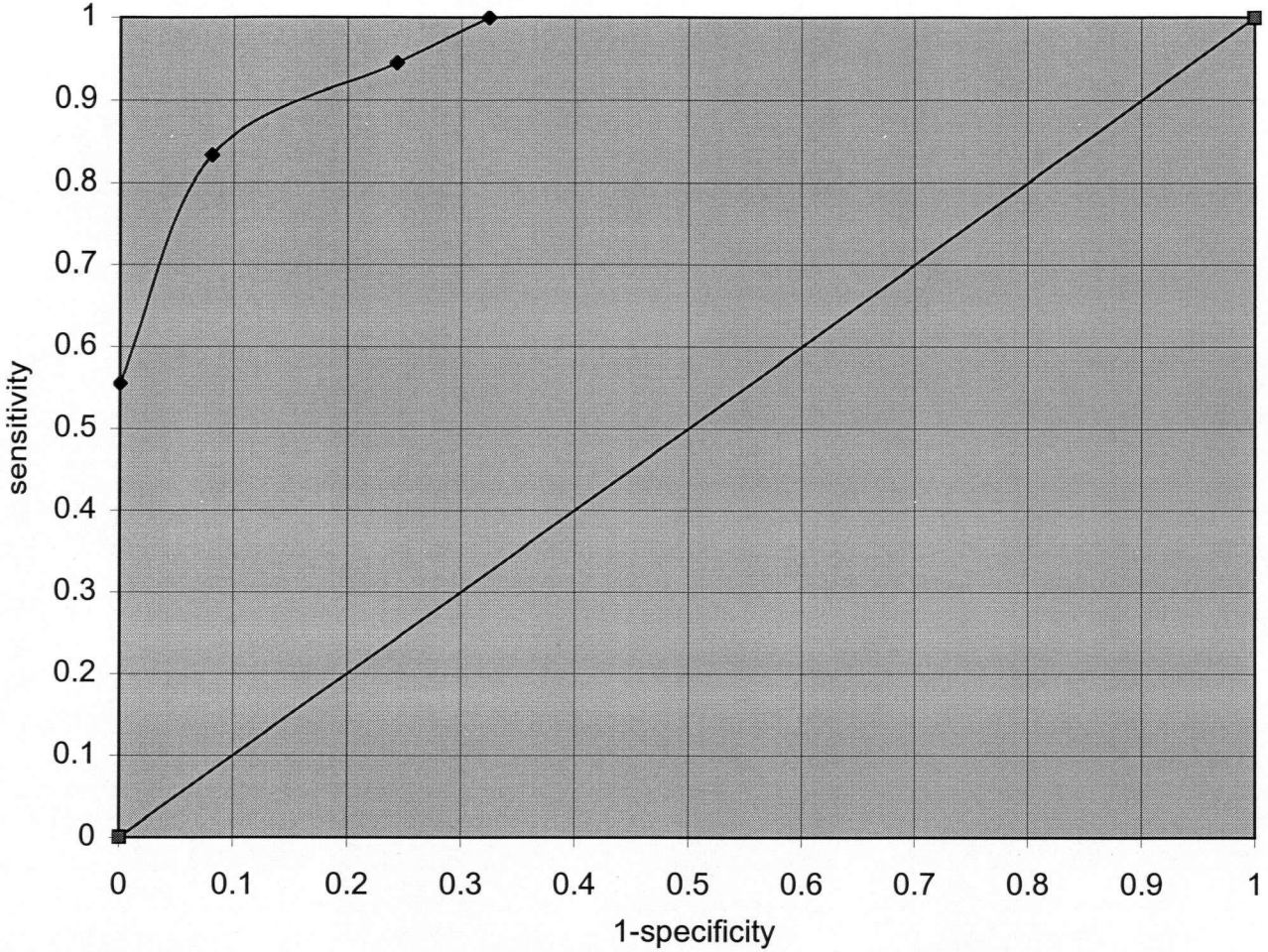

Figure 22. The ROC curve of (70%-R)DLCO/VO2 for prediction of overall complications. The solid line is the line for a test with no discrimination. The AURC was 0.95; the best cut pont was 4 (ml/min/mmHg)/(L/min) with sensitivity 83% and specificity 92%.

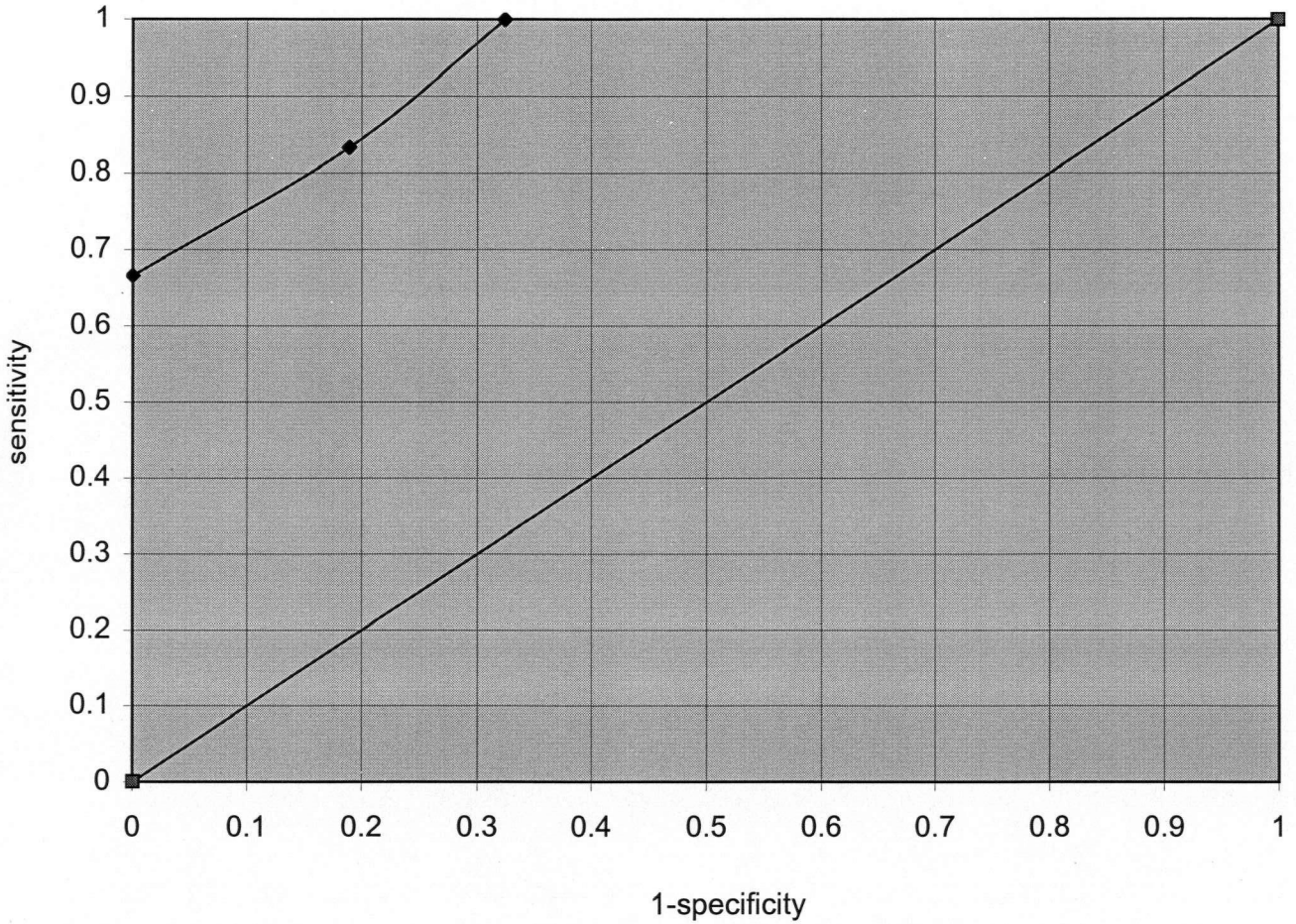

Figure 23. The ROC curve of (70%-R)DLCO/VO2% for prediction of overall complications. The solid line is the line of identity for a test without any discrimination. The AURC was 0.94; the best cut point was 0.2 with sensitivity 67% and specificity 100%.

CHAPTER FOUR: DISCUSSION

The main finding of this study is that patients with complications had only a limited increase in 3EQ-DLCO during exercise, from rest to 70% of their maximal workload, when compared with patients without complications. The slope of the increase in 3EQ-DLCO with increasing VO2 in patients with complications was much less than that of patients without complications (Figure 15, 16). The results suggested that the best variable in predicting complications was the increase in 3EQ-DLCO from rest to 70% of maximal workload, expressed as % of predicted resting SB-DLCO, (70%-R)DLCO%, as shown in Table VIII and IX; the best cut-off limit in predicting complications was < 10% (Table X). Expressing the increase in DLCO as a ratio to the increase in VO2 did not improve the discrimination between patients with and without complications, or the ability to predict complications. The limited increase in 3EQ-DLCO during exercise in patients with complications probably reflects the alveolar capillary membrane destruction and the reduction in the pulmonary capillary vascular bed or limitation of cardiac output. The strong correlation between exercise diffusing capacity and postoperative complications was likely due to the contribution of a reduced pulmonary capillary bed to cardiopulmonary complications. Exercise DLCO appears to be useful as an additional test to improve prediction of postoperative morbidity following lung resection. This is the first study to demonstrate that measurement of DLCO during exercise, using the 3-equation technique, is useful in evaluating patients with lung cancer prior to lung resection and in predicting postoperative cardiopulmonary complications.

Wound infection, hematoma, empyema, bronchopleural fistula, air leak greater than 7 days, and recurrent laryngeal nerve injury were regarded as technical morbidity, and were not considered as postoperative cardiopulmonary morbidity in this study. Our retrospective review of complications after pneumonectomy indicated that technical morbidity was not related to patients' lung function, but might be due to other factors such as surgical and anesthetic techniques, and perioperative care [Wang et al, 1999]. In this prospective study, the postoperative complication rate was 33% and the mortality rate was 4%, similar to recent previous reports [Kadri and Dussek, 1991; Miller, 1993; Damhuis and Schutte, 1996], and similar to the mortality rate of 5% in our review of 151 pneumonectomy cases [Wang et al, 1999]. This complication rate which is considered acceptable compared with recent literature and the low mortality rate are probably due to advances in preoperative assessment, anesthetic and surgical techniques, and postoperative care. Although cardiac arrhythmia was the major cause of morbidity, pulmonary edema was the major cause of mortality in this study (Table IV) and in our retrospective review [Wang et al, 1999]. Pulmonary edema and cardiac dysrhythmias may be induced by the supraphysiological stresses imposed on the heart and lung during surgery and postoperatively, and by hyperperfusion of the remaining pulmonary vascular bed.

Pulmonary edema

Fry had previously shown that endothelial injury could be induced by exposure to the

high shear stresses associated with increased blood flow rates with a nontraumatic intra-aortic device designed to produce a rapid convergence of the aortic blood stream into a narrow channel along the ventral aspect of the thoracic aorta in dogs [Fry, 1968]. He also suggested that the tensile stress in capillary walls from the increased perfusion pressure could cause vessels to rupture. West et al [West et al, 1991] raised pulmonary capillary pressure in anesthetized rabbits, and reported that disruption of the endothelium and alveolar epithelium were seen in some locations at capillary transmural pressure $\geq$ 40mmHg. The severity of the injury was proportional to the amount of transmural pressure applied. Platelets and leukocytes were often seen in close proximity to segments of the basement membrane that were exposed by breaks in the endothelium. In addition, increasing the tidal volume resulted in increased edema formation [Bshouty and Younes, 1988], as demonstrated in in-situ canine left upper lobe preparations, in which edema was induced by increasing blood flow 4-8 times normal. Hernandez et al [Hernandez et al, 1988] showed that, in mechanically ventilated anesthetized young rabbits, volume distension of the lung rather than high peak inspiratory pressure resulted in microvascular injury and increased permeability, and restricting chest wall motion reduced the extent of the lung in jury. Carlton et al [Carlton et al, 1990] evaluated lung lymph in young lambs and demonstrated that ventilation with high tidal volumes increased lymph flow and protein concentration, and concluded that lung overexpansion increased pulmonary microvascular protein permeability. Thus, it can be seen that increased flow and pressure within the pulmonary microvascular bed, ventilation with high tidal volumes, and overexpansion of the lung, can damage the alveolar endothelium and epithelium, leading to high permeability pulmonary edema.

The alveolus is supported by the interstitial connective tissue of the lung, and capillaries course through alveolar walls that are reinforced by discrete bundles of collagen and elastin [Sobin et al, 1988]. The capillary endothelium is encased in a thin basement membrane that is shared by the alveolar epithelium. Hyperinflation of an emphysematous lung may rupture damaged alveolar walls or emphysematous areas. Hyperperfusion of the pulmonary microvascular bed may damage the endothelium by increasing the fluid shear on the endothelium [Ohkuda et al, 1978]. Furthermore, capillary distension stretches the endothelium and reduces its ability to accommodate shearing forces. Capillary distension also increases the tension in the overlying alveolar epithelium. The stress of surgery can cause demargination and activation of neutrophils, which may be sequestered and retained in the lung [Lien et al, 1987; Markos et al, 1990], and this could lead to increased pulmonary artery pressure [Patterson et al, 1989]. The attachment and detachment of neutrophils from capillary walls can cause further disruption of the endothelium [Schmid-Schoenbein et al, 1975]. Stress failure of the alveolar epithelium and endothelium results in high permeability pulmonary edema. The protein in the edema fluid combines with surfactant and interferes with its function [Seeger et al, 1985], increasing surface tension, which favors the accumulation of even more pulmonary edema [Albert et al, 1979]. Furthermore, with severe stress injury, the endothelium becomes detached from the basement membrane, platelets and leukocytes are attracted to the site of injury and set up an inflammatory reaction. Inflammatory mediators such as platelet-activating factor are released and cause further tissue injury [Chang, 1992; Hamasaki et al, 1984; Patterson et al, 1989]. In addition, a damaged epithelium may prevent effective clearance of the alveolar edema [Matthay and Wiener-Kronish,

1990].

Cardiac dysrhythmias

Hsia et al [Hsia et al, 1990] found that the pulmonary artery pressure-flow relationship was not significantly altered by pneumonectomy in dogs during exercise, suggesting that pulmonary vascular resistance was essentially unchanged and that increases in pressure were primarily due to increased flow. However, cardiac output at any given work was lower after pneumonectomy, due to a reduced stroke volume which they attributed in part to an increased afterload. Reed et al [Reed et al, 1992] studied 15 patients during and after pulmonary resection, using a Swan-Ganz catheter and the thermodilution cardiac output method. They found that by the second postoperative day, pulmonary artery pressure and right ventricular end-diastolic volume increased, while right ventricular ejection fraction decreased [Reed et al, 1992]. Thus it can be seen that extensive lung resection may lead to pulmonary hypertension, elevated right ventricular end-diastolic pressures, and decreased right ventricular stroke volume.

Under conditions of pulsatile flow, the vascular impedance, which includes frequency-dependent components arising from the inertance of the blood and the compliance of the precapillary and postcapillary vessels, provides a more accurate description of the ventricular afterload [Piene, 1986]. When a volume of blood is injected by the contracting ventricle, some work must be done to overcome the inertia of the blood. As the bolus of blood travels through the precapillary vascular bed, some energy is expended in stretching the vessel walls. In addition,

part of the pressure wave is reflected at each point of bifurcation. This reflected wave interferes with the incoming wave and causes further energy losses [Fitchett, 1991]. Therefore, not all of the work done by the contracting ventricles is converted into the kinetic energy of blood flow. The mechanical efficiency, which can be defined as the ratio of kinetic energy of blood flow to the total work done by the ventricle in ejecting a given volume of blood, is optimized when there is impedance matching between the right ventricle and its output impedance [Kussmaul et al, 1992]. After extensive resection, the increased flow through the remaining vascular bed results in near-maximal recruitment of the capillaries. Therefore, pulmonary vascular resistance becomes fixed and pulmonary artery pressure increases linearly with the cardiac output. In addition, pulmonary vascular compliance is decreased. The right ventricle must try to match the new output impedance in order to optimize its mechanical efficiency. One way of accomplishing this is by reducing the stroke volume. This minimizes the energy lost in distending a noncompliant pulmonary vascular bed. Cardiac output is then increased primarily by increasing the heart rate. These pulmonary hemodynamic change result in increased wall stresses in the right atrium and right ventricle. By applying Laplace's law, it can be seen that the relative increases will be larger in the right atrium since it has a smaller wall thickness to chamber radius ratio than the right ventricle. It is well-known that ventricular dysrhythmias can be induced by over-distending the ventricle [Hansen et al, 1990]. This is thought to be due to the stretch-activation of mechano-sensitive membrane ion channels which cause an increase in the intracellular calcium [Stacy et al, 1992]. The increased intracellular calcium lower the threshold for membrane depolarization and leads to dysrhythmias. Mechano-sensitive potassium channels have now been identified in atrial myocytes [van Wagoner , 1993]. Therefore, it is conceivable that atrial dysrhythmias may

arise from increased wall stresses in a manner analogous to that observed for ventricular dysrhythmias.

METHODS USED TO EVALUATE PATIENTS PRIOR TO LUNG RESECTION

Clinical evaluation

Clinical factors (including dyspnea scale, exercise capacity, performance status, surgical intervention, surgical approach, and final diagnosis) discriminated between patients with and without cardiopulmonary complications in this study, but not as well as age and history of COPD (Table V). The extent of surgical intervention was also a significant factor related to mortality as well as complications; the two mortality cases had either pneumonectomy or bilobectomy, and all cases with complications had either pneumonectomy or lobectomy. Moreover, all 13 patients who had segmentectomy or a lesser resection did not have any complications. This suggests that the amount of parenchyma resected is related to the development of postoperative complications including mortality, and supports the conventional approach to perform the minimal resection possible. Many other clinical factors have been identified, however, that may increase the risk of postoperative complications: pulmonary dysfunction, chronic productive cough, cigarette smoking, advanced age, respiratory infections, prolonged anesthesia, and obesity. These clinical factors alter four major aspects of patient's respiratory status: lung volume, ventilatory pattern, gas exchange, and respiratory defense mechanisms [Dunn and Scanlon, 1993].

Sedatives and narcotics may blunt the sigh mechanism and thus promote atelectasis postoperatively. The development of atelectasis increases dead space ventilation and the work of breathing, and impairs O2 gas exchange. Because physiologic dead space is unchanged or increased and tidal volume is decreased as a result of sedation, the ratio of dead space to tidal volume is increased. Atelectasis and small airway closure impair gas exchange by ventilation-perfusion mismatching, leading to right-to-left intrapulmonary shunting and increased dead space ventilation. Bacterial adherence to upper airway epithelium may be altered after instrumentation. Mucociliary clearance is adversely affected by anesthesia and local factors. Clearance of secretions from the airway is reduced when coughing is abolished by sedative, analgesic, and anesthetic agents. These drugs may also predispose postoperative patients to aspiration of gastric or oral contents.

Lung function testing

Lung function testing showed significantly lower FEV1% predicted, FVC% predicted, and FEV1/FVC in our patients with complications than in those without complications (Table VI). Our analysis showed that spirometry for preoperative evaluation was still a simple and useful predictor of complications. The ability of lung function testing to predict postoperative complications has been variable in previous studies. Patient selection, sample size, choice of endpoints, and the retrospective design of some studies are among the possible reasons for the variable reports. Even in the presence of significantly impaired lung function, most respirologists would err on the side of recommending lung resection for lung cancer in borderline cases,

because a decision not to operate almost always will result in death from progressive cancer.

DLCO

DLCO% predicted and DLCO/VA% predicted were significantly lower in patients with complications than patients without complications in this study (Table VI). DLCO is predicted based on gender, age, and height. A normal DLCO/VA can be misleading by implying that pulmonary capillary loss in proportion to lung volume loss (i.e. a low DLCO and low VA with normal DLCO/VA) reflects a normal pulmonary capillary bed [MacIntyre, 1997]. Thus, DLCO/VA may not be as good a discriminator as DLCO in evaluating lung diffusion preoperatively. Our retrospective study [Wang et al, 1999] and this study showed that DLCO% predicted was better than DLCO/VA% predicted in its correlation with postoperative complications (Table VI).

Factors that increase DLCO include exercise, anxiety, a previous deep breath [Lebecque et al, 1995], prolonged breath holding at RV before performing the test [Lebecque et al, 1986], the supine or the 15 degree head down position, microgravity [Prisk et al, 1993], and high negative pressure during inspiration. Factors that decrease DLCO include a Valsalva maneuver, decreased hemoglobin, increased carboxyhemoglobin concentration, and increased ambient oxygen tensions. Since a number of factors, including inspiratory and expiratory flow, breath-holding time, and equipment, affect DLCO, reproducibility between laboratories has been poor even in normal subjects [Kangalee and Abboud, 1992]. However, the reproducibility of DLCO is

expected to improve if laboratories follow the ATS guidelines for standardization of the technique [ATS, 1995]. The 3EQ-DLCO technique offers an advantage compared with the standard SB-DLCO technique, since it is independent of flow rate and breath-holding time, and its reproducibility and accuracy is better than the standard DLCO [Graham et al, 1981 and 1995].

Radionuclide lung scanning

Only a few of our patients had quantitative radionuclide lung scanning. However, this technique has been studied in the literature [Larsen et al, 1997] and found to be useful in preoperative evaluation, especially prior to pneumonectomy, and in estimating the predicted postoperative FEV1 and DLCO. One would expect that such a determination based on the extent of pulmonary resection, the preoperative FEV1, the preoperative DLCO, and the proportion of perfusion of the lung resected, would be the preferred method. A new index, designated the predicted postoperative product, obtained by multiplying the % of predicted postoperative FEV1 by the % of predicted postoperative DLCO, was found by Pierce et al [Pierce et al, 1994] to have the strongest predictive ability for mortality.

The predicted postoperative product is a new concept including values of ventilatory function (FEV1), gas transfer (DLCO), lung perfusion (lung scan), and the resected lung into a single index. This index allows a patient with a value below the threshold for one criterion based on FEV1 or DLCO to be accepted for surgery on the basis of a good value in the other. Because this index uses % predicted rather than absolute values for FEV1 and DLCO, it can apply to

patients of either gender across a wide range of age, and height. A value < 1650 by this index was predictive of 7 of 8 deaths in the series of Pierce [Pierce et al, 1994] and of all 3 of the deaths in the series of Markos [Markos et al, 1989], so values <1650 could be considered as indicating a high risk of mortality. In our study, radionuclide scanning was performed as part of the preoperative evaluation in only a few cases (but not in the mortality cases), so we could not evaluate it in predicting complications.

Progressive exercise testing

Progressive exercise testing demonstrated that maximal workload, VO2max% maximal predicted, VO2max/kg, and O2 pulse at maximal workload were significantly lower in patients with complications than patients without complications in this study (Table VII). The purpose of the exercise test is to stress the entire cardiopulmonary oxygen delivery system and estimate the physiologic reserve that may be available after lung resection. During exercise, the lung increases ventilation, O2 uptake, CO2 output, and blood flow simulating increased demands in the remaining lung after lung resection. An oxygen deficit leading to organ failure and death may occur postoperatively. Cellular function depends on adequate delivery of oxygen and nutrients to the tissue and subsequent removal of carbon dioxide and waste chemicals. The viability of the entire system during exercise requires interaction between the lungs, heart, blood vessels, and peripheral muscles.

When cellular respiration increases, there is a predictable increase in the rate of VO2;

total body VO2 is related to the age of patient, the type of work, gender, and body weight. At some point, a plateau may develop resulting in VO2max, after which, further increases in workload are not associated with a continued rise in VO2. A normal person can increase VO2 maximally as a result of maximal interaction between the exercising muscles, and the cardiovascular and ventilatory systems. A low VO2max can be accounted for by a variety of disorders including anemia, heart disease, metabolic disease, neuromuscular disorders, peripheral vascular disease, and pulmonary disease, or just poor effort. Detailed analysis of further information from exercise testing helps to investigate the nature of underlying disorders causing a reduced VO2max.

3EQ-DLCO DURING EXERCISE

Potts et al. [Potts et al, 1996], using the same 3EQ-DLCO equipment, determined 3EQ-DLCO in 11 normal, healthy subjects at the levels corresponding to 25%, 50%, 75%, and 90% of their maximal workload from progressive exercise testing. They showed an increase in 3EQ-DLCO% predicted from 129±3% at rest to 187±5% at 75% and 198±5% at 90% of their peak power output; their subjects were generally fit and young. In our patients without complications, 3EQ-DLCO% predicted increased from 102±27% at rest to 136±33% at 70% of the patients' maximal workload, but our patients were older (61±11 versus 29±2 yr), and their VO2max% maximal predicted (70±13%) was lower than the normal subjects studied by Potts et al (115±6%)[Potts et al, 1996]. Moreover, the subjects in the Potts study had a higher 3EQ-DLCO% predicted (129±3%) at rest than our patients without complications (102±27%) which is

likely due to the effects of smoking and the presence of lung disease in our patients.

3EQ-DLCO is affected by the lung volume from which the 3EQ-DLCO maneuver is initiated, and lung volume may change during exercise in patients with severe COPD [O'Donnell et al, 1998]. Although 41% of our patients had past history of COPD, most of them had a mild or moderate degree of obstruction. The resting IC in patients with COPD was not statistically different from IC at 70% of maximal workload (2.90±0.55 versus 3.06±0.63 L). Similarly, there were no significant differences in the 3EQ-DLCO expiratory VC (3.39±0.71 versus 3.62±0.81 L), alveolar volume (5.98±0.88 versus 5.92±0.88 L), RV (2.89±0.58 versus 2.74±0.44 L), inhalation time (1.69±0.68 versus 1.43±0.56 second), breath holding time (2.37±0.78 versus 1.87±0.75 second), exhalation time (4.21±1.29 versus 3.85±1.27 second) in the patients with COPD, when done at rest and during exercise at 70% maximal workload. The changes from resting IC to IC at 70% of maximal workload in patients with COPD were not statistically different from patients without COPD (0.16±0.15 versus 0.16±0.21 L). Similarly, changes in expiratory VC (0.11±0.14 versus 0.23±0.31 L), alveolar volume (0.14±0.17 versus 0.06±0.14 L), RV (0.11±0.15 versus 0.15±0.23 L), inhalation time (0.17±0.23 versus 0.26±0.42 second), breath holding time (0.18±0.35 versus 0.50±0.79 second), exhalation time (0.45±0.85 versus 0.36±0.56 second) from rest to 70% of maximal workload in patients with COPD, were not statistically different from those without COPD. Therefore, 3EQ-DLCO studies during exercise in our patients with COPD were not affected by changes in IC or lung volumes during exercise.

Resting 3EQ-DLCO% predicted, 3EQ-DLCO during exercise at 70% of maximal

workload (70%DLCO% predicted), and the increase in 3EQ-DLCO with exercise ((70%-R)DLCO%) were significantly lower in patients with complications than patients without complications in this study (Table VII). The strong correlation between exercise diffusing capacity and postoperative complications is likely due to increased cardiopulmonary complications in patients with a reduced pulmonary capillary bed, lower available alveolar tissue, and poor recruitment of pulmonary capillary blood volume. Furthermore, 70%DLCO% predicted, and (70%-R)DLCO% were significantly lower in patients with mortality than patients without mortality in this study. Therefore, (70%-R)DLCO appeared to be a predictor for postoperative mortality in this study, but due to the small number cases, this will require validation in a larger study.

The conventional SB-DLCO uses a single equation that is valid only for the breath holding phase of the maneuver, and may be affected by inhaled and exhaled flow, breath holding time, and the size and timing of the alveolar sample collection [Graham et al, 1981]. However, 3EQ-DLCO is independent of such factors, and improves the accuracy and precision of the measurement in patients with airflow obstruction [Graham et al, 1984]. Using 3 separate analytic equations to describe CO uptake during the 3 phases of the DLCO maneuver (inhalation, breath-holding, and exhalation) eliminates these errors and removes the constraint of performing a breath-holding maneuver for 8-10 seconds that is difficult for subjects to perform during exercise. These advantages of the 3EQ-DLCO technique, may help its potential value in expanding its use in the future, especially during exercise, with the more ready availability of rapidly responding CO and CH4 analysers and the required computerized software.

COMPARISON OF THE VARIABLES USED FOR PREOPERATIVE EVALUATION

Boxplots analysis of the 4 variables ((70%-R)DLCO%, DLCO% predicted, VO2max/kg, and FEV1% predicted) for complications (Figure 7-9), indicated that (70%-R)DLCO% was the most significant variable to discriminate between patients with and without complications. Further analyses using logistic regression models (Table VIII) and ROC curves with AURC determinations (Figure 11-14 and Table IX), showed that (70%-R)DLCO% was the best predictor of complications, followed in decreasing order by DLCO% predicted, VO2max/kg, and FEV1% predicted. The same analysis showed that the type of complications that was best predicted by (70%-R)DLCO% was overall complications, followed in decreasing order by pulmonary morbidity, cardiovascular morbidity, and mortality (Figure 10). Our retrospective review of complications following pneumonectomy also showed that DLCO% predicted was a better predictor of complications than FEV1% predicted [Wang J.-S. et al, 1999]. A recent study from Chicago also concluded that showed DLCO% predicted was a better predictor than VO2max/kg [Wang J. et al, 1999]. Another study suggested that the addition of invasive measurement of pulmonary artery pressure during exercise and exercise testing were not helpful in preoperative assessment [Ribas et al, 1999]. The index (70%-R)DLCO% was derived from the combination of DLCO measurement and progressive exercise testing, and therefore may be expected to be better than either alone. The preoperative variables used in our assessment were mainly related to the lung, and therefore this may explain our finding that pulmonary morbidity was better predicted than cardiovascular morbidity.

The best cut-off limit for (70%-R)DLCO% in predicting postoperative complications was 10% (Table X). The best cut-off limit for DLCO% predicted in predicting postoperative complications was 70% confirming the finding of our retrospective review [Wang et al, 1999]. The best cut-off limit for VO2max/kg in predicting postoperative complications was 15ml/kg/min confirming the findings of previous studies of exercise testing [Morice et al, 1992; Gilbreth and Weisman, 1994]. The best cut-off limit for FEV1% predicted in predicting postoperative complication predictions was 80%; this high level of FEV1 might be due to selection of patients with good FEV1% predicted for lung resection, since FEV1 was still the main traditionally used test for preoperative lung function evaluation. In addition to the extent of surgical intervention as a risk factor, (70%-R)DLCO% was also a significant predictor of postoperative mortality, and the best cut-off limit of (70%-R)DLCO% in predicting postoperative mortality was 5%.

Further analysis evaluating the increase in DLCO with exercise as a function of the increase in VO2 (Table VII-X and Figure 15-23) indicated that, (70%-R)DLCO/VO2 and (70%-R)DLCO/VO2% were also useful predictors. However, as a discriminatory index, (70%-R)DLCO% was similar to either (70%-R)DLCO/VO2 or (70%-R)DLCO/VO2%, and was simpler to obtain since it did not require measurement of VO2 at resting or during exercise. The indices (70%-R)DLCO/VO2 and (70%-R)DLCO/VO2% were better at predicting complications than the other three preoperative variables (DLCO% predicted, VO2max/kg, and FEV1% predicted) in all aspects. In our study, patients with complications had more frequently a history

of COPD and were older than patients without complications. The alveolar tissue destruction and pulmonary capillary loss due to emphysema resulted in a low DLCO and reduced pulmonary capillary bed; a poor cardiovascular system associated with old age could lead to an inadequate increase in DLCO during exercise because of reduced cardiac output and decreased recruitment of pulmonary capillaries. If there is more impairment in exercise cardiac output and VO2 during exercise than impairment in the increase of DLCO with exercise, the ratios of (70%-R)DLCO/VO2 and (70%-R)DLCO/VO2% would not decrease relatively as much as (70%-R)DLCO%. Under these circumstances, (70%-R)DLCO% may be expected to be better than (70%-R)DLCO/VO2 and (70%-R)DLCO/VO2% in predicting postoperative complications in our study.

Changes in alveolar capillary membrane and in pulmonary capillary blood volume producing a reduction of DLCO in emphysema may be due to destruction of the pulmonary capillary bed [Bedell and Eggers, 1964], loss of lung tissue [Pecora et al, 1968], or decrease in the surface area or increase in the thickness of the alveolar capillary membrane [Jain et al, 1972]. Although the DLCO at rest is sensitive enough to detect emphysema, it is not sensitive enough to detect mild emphysema [Morrison et al,1990]. Thus, in the face of mild disease with slight reduction in alveolar capillary surface, the remaining capillaries with their ability to distend might be recruited to replace capillaries involved in the emphysematous lesion, yielding a normal value for DLCO [Spencer, 1985]. In such patients, measurements of DLCO during exercise may detect the abnormally reduced alveolar capillary surface and improve the sensitivity of the DLCO for the detection of emphysema as suggested by Gelb et al [Gelb et al, 1973].

Patients with COPD often complain of exercise intolerance; reduced cardiac output can contribute to limited exercise capacity in patients with severe COPD [Killian et al, 1992]. The tight link between cardiac output and VO2 is usually preserved even in the face of severe COPD; at peak exercise, maximal cardiac output is reduced to about 50% of what a normal older subject could achieve at peak exercise, mainly because of ventilatory capacity limiting peak exercise [Dantzker and D'Alonzo, 1986; Stewart and Lewis, 1986; Agusti et al, 1990]. Therefore, the control of cardiac output during exercise in COPD may remain regulated to match the level of exercise and VO2 achieved; however, cardiac function may be compromised and a higher cardiac output may not be achieved if there is pulmonary hypertension. Pulmonary hypertension is often evident even at rest, and is usual during exercise in patients with severe COPD [Dantzker and D'Alonzo, 1986]. In such patients, vascular resistance remains constant or may even rise during exercise [Agusti et al, 1990]. Therefore, some patients with emphysema may have a lower increase in DLCO during exercise due to decreased recruitment of pulmonary capillary blood volume from a reduced cardiac output during exercise.

FURTHER CONSIDERATIONS

The extent of pulmonary resection a patient can tolerate should be determined preoperatively and is based on both pulmonary function testing and the patient's performance status. The size and location of the lesion by CT scan of the chest, and bronchoscopy are helpful in determining how much lung will be required for complete resection. Once the amount of lung that required resection is determined and the FEV1 and DLCO have been assessed, the surgeon

must decide if the patient can tolerate resection. Prophylactic interventions may be used to decrease the risk of perioperative morbidity or mortality. Preoperative prophylactic interventions include smoking cessation, breathing training, antibiotics, expectorants, bronchodilator therapy; and weight reduction. Intraoperative management includes limited anesthesia and thoracotomy times, intermittent hyperinflation to prevent atelectasis, better control of secretions, prevention of aspiration, and maintenance of bronchodilatation. Postoperative measures include incentive spirometry, mobilization of secretions, early ambulation, cough encouragement, and adequate pain control.

There have been significant advancements in understanding cardiopulmonary physiology, surgical technique, perioperative care, and nonsurgical treatment modalities [Marino et al, 1994]. Hypercapnia as a barrier to lung resection has been overcome by successfully resecting lung tissue of selected patients in chronic respiratory failure [Morice et al, 1992; Kearney et al, 1994; McKenna, 1994]. Video-assisted thoracoscopic surgery may minimize postoperative thoracic cage impairment and may further reduce perioperative complications [McKenna, 1994]. Lung volume reduction surgery at the same time as surgery for lung cancer can improve recovery of postoperative lung function [Cooper et al, 1995]. Anesthetic agents with minimal respiratory and cardiac depression have led to early extubation, which avoids tracheobronchitis and nosocomial infection from prolonged mechanical ventilation. Epidural anesthesia has helped reduce postoperative pain and enables patients to clear secretions by improved cough, ability to generate deep inspirations, and early ambulation. Nonsedating analgesics are often used as a supplement to epidural analgesia, thereby, further reducing the risk of hypercapnia in these patients who are

prone to carbon dioxide retention. Minitracheostomy, which is a percutaneous tracheal catheter inserted at the bedside, allows for easy suctioning without the morbidity of formal tracheostomy [Thomas et al, 1995]. The increased availability of oxygen saturation monitors enables one to frequently assess the patient's respiratory status without the need for repeated artery blood gas sampling or an intensive care unit setting.

Patients with lung cancer have a disease with ultimately 100% mortality when left untreated and if nonoperative therapy is ineffective. Lung resection, the best and potentially curative therapy, carries risks, especially when performed on elderly patients with coexistent cardiopulmonary disease. Our study suggests that the use of exercise diffusing capacity in preoperative assessment as an additional test prior to lung resection, will help define patients at increased risk, for whom increased effort at postoperative care may help to reduce morbidity and mortality. This approach requires further testing on a larger numbers of patients and in other centers.

Patients whose lung function is below the safe preoperative limits for lung resection should not be completely rejected for surgical therapy, because without surgery the outlook for lung cancer is poor. They should be on intensive therapy to improve lung function. They should be counseled as to the risks of death or prolonged disability from surgery, given other treatment options, and offered an attempt at resection using all the postoperative management skills if the risk for surgery is not considered prohibitive. However, the previous concept of threshold values for preoperative variables should be applied cautiously, especially since lung volume resection

surgery for emphysema applied at the same time as surgery for lung cancer [Cooper et al, 1995] may enable patients with poor lung function due to emphysema to undergo surgery for limited lung cancer. [McKenna et al, 1996].

Through the improvement of computerized pulmonary function equipment and the refinement and availability of rapidly responding gas analyzers for CO and CH4, it will be possible in the near future to use commercial pulmonary function systems to perform 3EQ-DLCO. 3EQ-DLCO measurement without breath-holding, can be done equally well by normal subjects and by patients with lung disease both at rest and during exercise. Technical progress in this area, may result in further application of the use of the 3EQ-DLCO during exercise in evaluating lung function and in the preoperative assessment of patients scheduled for lung resection.

CHAPTER FIVE: CONCLUSIONS

1. 3EQ-DLCO can be used to measure DLCO during exercise in patients with lung cancer prior to lung resection.
2. 3EQ-DLCO increases with steady state exercise in patients without complications, but does not substantially increase in patients with complications. The mean increase in 3EQ-DLCO from rest to 70% of maximal workload expressed as % of predicted resting SB-DLCO, (70%-R)DLCO%, was significantly lower ($p<0.001$) in patients with complications than patients without complications (5 ± 9 versus $34\pm14\%$). The best cut-off limit was 10% for the index (70%-R)DLCO%, with a sensitivity of 78% and a specificity of 100% in predicting overall complications.
3. The strong correlation between exercise diffusing capacity and postoperative complications is likely due to reduction in the pulmonary capillary bed and loss of alveolar lung tissue contributing to cardiopulmonary complications.
4. Exercise DLCO appears to be useful as an additional test to improve the prediction of postoperative morbidity following lung resection.
5. Although cardiac arrhythmia is the major cause of morbidity, pulmonary edema is the major cause of mortality.
6. (70%-R)DLCO%, in association with the extent of surgical resection, may be useful in assessing the risk of predictors of postoperative mortality, but this will require evaluation of a larger number of patients.

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ABBREVIATIONS

ATS	American Thoracic Society
AURC	area under ROC curve
COPD	chronic obstructive pulmonary disease
CT	computed tomogram
DL	lung diffusing capacity
DLCO	CO pulmonary diffusing capacity
70%DLCO	3EQ-DLCO at 70% of maximal workload
EKG	electrocardiogram
3EQ-DLCO	three-equation CO lung diffusing capacity
FEV1	forced expiratory volume in 1 second
FRC	functional residual capacity
FVC	forced vital capacity
GOT	glutamic oxaloacetic transaminase
IC	inspiratory capacity
RDLCO	3EQ-DLCO at rest
(70%-R)DLCO%	the value of 70%DLCO% predicted minus RDLCO% predicted
(70%-R)DLCO/VO2	ratio of 70%DLCO minus RDLCO to the same change in VO2
(70%-R)DLCO/VO2%	ratio of (70%-R)DLCO% to the same change in VO2
ROC	receiver operating characteristic

RV	residual volume
SB-DLCO	single breath CO lung diffusing capacity
TLC	total lung capacity
VC	vital capacity
VO2	oxygen consumption
VO2max	maximum oxygen consumption

APPENDIX I: 3EQ-DLCO ALGORITHM

The three-equation algorithm uses 3 separate equations to describe CO uptake, i.e. 3EQ-DLCO, through each phase of the single breath breathing maneuver. The three mass balance equations are

for inhalation:

$$V_A(t)*dF_ACO(t)/dt+F_ACO(t)*dV_A(t)/dt = -DLCO(t)*(PB-47)*F_ACO(t)+F_ICO(t)*dV_A(t)/dt \quad [8]$$

for breath holding (the Krogh equation):

$$V_A(bh)*dF_ACO(t)/dt = -DLCO*(PB-47)*F_ACO(t) \quad [9]$$

and for exhalation:

$$V_A(t)*dF_ACO(t)/dt = -DLCO*(PB-47)*F_ACO(t) \quad [10]$$

where $V_A(t)$ is the alveolar volume at time t, $F_ACO(t)$ is the fractional alveolar concentration of CO at time t, $F_ICO(t)$ is the fractional inspired concentration of CO at time t, PB is the barometric pressure, and $V_A(bh)$ is the alveolar volume during breath holding [Graham et al, 1981].

APPENDIX II: UNIVERSITY OF BRITISH COLUMBIA & VANCOUVER GENERAL HOSPITAL ETHICS APPROVALS

APPENDIX III: RECRUITMENT LETTER FOR SUBJECTS

APPENDIX IV: CONSENT FORM

Study Procedures:

The study procedure consists of measuring my diffusing capacity with a modified technique which enables the measurement to be done without breathholding. It is planned to measure the diffusing capacity at rest, and at two levels of exercise, equivalent to 35% and 70% of my maximum exercise capacity on an electronic exercise bicycle. First my diffusing capacity will be measured at rest. Then I will have a progressive exercise test to determine my maximal exercise capacity. I will start exercising at a low workload on an electronic stationary exercise bicycle, and the workload will be increased by a small increment every minute until I reach my maximum exercise capacity. My electrocardiogram, breathing, O_2 uptake and CO_2 production, blood pressure, dyspnea scale, and oxygen saturation will be monitored continuously during exercise testing. The exercise testing will be stopped if I feel unduly short of breath, my oxygen saturation drops significantly, or my heart rate increases to over 90% of the predicted maximum exercise heart rate for my age.

After a rest period of 30 minutes, I will have testing of my diffusing capacity at rest and at two levels of exercise, equivalent to 35% and 70% of my maximum exercise capacity on an electronic exercise bicycle. Each level of exercise will be maintained for about 3 min to allow heart rate and lung function to be stable prior to measuring diffusing capacity. During the measurement I will be asked to take a deep breath in, hold my breath for 1 to 2 seconds, and then breathe out following the pattern shown on a video monitor. The test will be done twice at each level of exercise. I will rest for about 15 minutes between the two levels of exercise.

Total time involved for the test is about 2-3 hours, including rest periods in between the tests.

Exclusions:

I will be excluded if I have heart disease preventing me from exercising, if my resting oxygen saturation is below 90%, if my bronchial tubes are severely obstructed, if my breathing capacity is severely reduced, if I am a current smoker, if I am over 85 years old, or if I have physical impairment preventing me from exercising.

Side Effects:

The modified diffusing capacity test by itself will not have any side effects. I am aware that I may feel short of breath during exercise testing, but that should be quickly relieved after the exercise is completed. If my oxygen saturation decreases significantly, I will be given oxygen for a few minutes to correct my O_2 level. My heart rate and blood pressure will go up with the exercise, but that should recover promptly after testing. My ECG will be continuously monitored during the test and the test will be stopped if there is a significant abnormality. Side effects such as irregular heart beat or chest pain may occur occasionally but will be temporary; serious side effects or risks are very unlikely. Patients with heart disease preventing them from exercising will be excluded from the study, so it is unlikely that I will have significant cardiac side effects from the study.

Benefits:

I will know my exercise capacity and will get a better idea of my breathing capacity. The study may help to improve preoperative evaluation of patients for lung resection, but may not be of direct benefit to me.

APPENDIX V: CLINICAL QUESTIONNAIRE

Clinical Questionnaire for Exercise DLCO Study

Date: _____ **Chart #:** _____ **PFT#:** _____

Name: _____
LAST FIRST MIDDLE INITIAL

Date of Birth (mm/dd/yy): _____ **Weight** (kg): _____ **Height** (cm): _____

Thoracic Surgeon: _____ **Date of Lung Resection:** _____

Telephone: _____ **Address:** _____

Clinical Symptoms:

A) Respiratory

1) Cough? N Y _____

2) Phlegm? N Y _____

3) Wheezing? N Y _____

4) Performance Status _____

5) Dyspnea Scale _____

6) Exercise Capacity _____

B) New York Heart Association Class and History of heart disease or hypertension? N Y

_____

C) History of any disease _____

_____

_____

_____

_____

_____

Smoking History:

Are you a current smoker? N Y Age started _____

Have you ever smoked regularly? N Y Age started _____ Age stopped _____

Number of years you smoked? _____ Cigarettes per day _____

Medications and Allergies:

_____

_____

_____

_____

_____

_____

Physical Examination:

BT: _____ BP: _____ Heart Rate: _____ Respiratory Rate: _____

A) Respiratory System:

B) Cardiovascular System:

C) Clubbing N Y

D) Edema N Y

APPENDIX VI: GAS ANALYSER LAG AND RESPONSE TIMES DETERMINATION

The lag time of a gas analyzer is the transport time of aspirated gas through the tubing to the sample chamber, whereas the response time is the time of the gas analyzer takes to register 90% of the maximal response signal. The lag and response times were determined by rapidly switching the gas being sampled from zero to full scale CO and CH4 while the change in flow from room air to test gas was measured simultaneously. A $\pm$ 225 cmH2O differential pressure transducer (Model "MP45-14-871"; Validyne, Northridge, CA) was used to detect sudden changes in gas pressure. The zero and span settings on the carrier demodulator were adjusted to within the range of the differential pressure transducer. A short sample tubing with a pressure release valve was used to connect the 3EQ-DLCO test gas mixture flowing at 12-15 l/min to the positive end of the pressure transducer. A three-way stopcock, placed between the test gas tank and the pressure transducer, directed the flow of test gas either towards the positive end of the differential pressure transducer, or to a cut-off syringe where the gas analyzers sampling continuously. The test gas flow was rapidly switched from the differential pressure transducer to the cut-off syringe allowing the gas analyzers to sample from zero to full scale CO and CH4 concentrations, while the sudden release of pressure on the differential pressure transducer gave an indication of the start of gas sampling. The response curves for the CO and CH4 analyzers, and the flow signal were displayed on a computer screen with moveable cursors to indicate the start and end points of the respective CO, CH4, and flow signals. The lag time of each gas

analyzers was determined from the time interval between the onset of pressure signal to the onset of the gas analyzer signal using the customized 3EQ-DLCO software program (designed by Dr. Brian L. Graham, University of Saskatchewan, Saskatoon). The 0-90% response time for each gas analyzer was determined by the software from the onset of the signal to the 90% of the maximal deflection, and the response times for the CO and CH4 analyzers were confirmed to be under 250 ms. The software simply added the lag and response times for each gas analyser, to adjust its timing with the flow and volume signal, in the 3EQ-DLCO calculations.

APPENDIX VII: PROGRESSIVE EXERCISE TESTING EQUIPMENT CALIBRATION

Calibration procedures were performed daily and verified before every exercise test. The barometric pressure and room temperature are continuously monitored by internal pressure and temperature sensors. For flow volume calibration, the 3 liters calibration syringe is connected to the mass flow sensor. Two strokes of the syringe are used to purge the mass flow sensor with room air. A ten-second timer is used for zeroing the mass flow sensor. This ensures that the air around the mass flow sensor has stabilized before the zero flow point is taken. Then, the flow volume calibration using two measurement sequences is combined into one continuous procedure. First, for the calibration sequence, a calibrated 3.0 liters volume syringe is connected to the mass flow sensor and 5 strokes are used to calibrate inspired and expired volumes. Correction factors are then calculated to fine-tune the volume measurement. Second, for the verification sequence, 5 strokes of the syringe are used to check the inspired and expired volumes using the newly calculated correction factors.

For analyser calibration, the two calibration gas tanks, (16% O2 and 4% CO2) and (26% O2 and 0% CO2), must be turned on completely, and the pressure gauges are set between 50 and 60 PSI. The sample line is connected to the calibration gas fitting on the front of the pneumatics module. Both O2 and CO2 analyzers will initially sample three gas connections (the two calibration gases, and room air) and calculate correction factors. The correction factors are then

verified by sampling the same three gases. The sample line is reconnected to the gas sample fitting on the mass flow sensor. All calibration points were verified and stored in the progressive exercise testing program.

APPENDIX VIII: COMPARISON OF RESULTS IN RELATION TO COMPLICATIONS FOR THE 44 CASES WHO HAD LOBECTOMY OR PNEUMONECTOMY

A. Clinical evaluation in relation to complications in the 44 cases

Variables	Complications (n=19)	No Complications (n=25)	p value
Age (yr)	70±6	63±11	<0.01
Chronic obstructive pulmonary disease (Y/N)	14/5	7/18	<0.01
New York Heart Association class (1/2)	18/1	20/5	NS
Dyspnea scale (0/1/2)	4/14/1	13/12/0	<0.05
Exercise capacity (1/2)	4/15	13/12	<0.05
Performance status (0/1)	4/15	13/12	<0.05
Surgical procedure			NS
Pneumonectomy	6	4	
Bilobectomy	1	1	
Lobectomy	12	20	
Intercostal space for surgery (3/4/5/6)	0/5/11/3	1/1/22/1	<0.05
Final diagnosis			<0.05
Lung cancer	19	19	
Metastatic cancer	0	5	
Benign lesion	0	1	

NS: not significant.

B. Preoperative lung function variables in relation to complications in the 44 cases

Variables	Complications (n=19)	No Complications (n=25)	p value
FEV1% predicted	72±14	87±19	<0.001
FVC% predicted	87±16	95±13	NS
FEV1/FVC (%)	64±11	71±11	<0.05
RV/TLC (%)	40±8 (n=17)	35±9 (n=21)	NS
DLCO% predicted	62±13 (n=17)	89±17 (n=21)	<0.001
DLCO/VA% predicted	74±23 (n=17)	92±17 (n=21)	<0.01

NS: not significant.

C. Preoperative exercise and 3EQ-DLCO variables in relation to complications in the 44 cases

Variables	Complications (n=19)	No Complications (n=25)	p value
Maximal workload (watt)	90±30	112±28	<0.01
VO2max% maximal predicted	57±14	70±13	<0.01
VO2max/kg (ml/kg/min)	15.0±2.4	18.3±3.7	<0.001
Maximal O2 pulse (ml/beat)	8.8±2.4	10.3±2.4	<0.05
3EQ-DLCO% predicted*	76±37	102±30	<0.01
70%DLCO% predicted*	83±40 (n=18)	137±33 (n=24)	<0.001
(70%-R)DLCO% (%)*	5±9 (n=18)	34±10 (n=24)	<0.001

*: predicted for 3EQ-DLCO is % predicted of resting SB-DLCO.

APPENDIX IX: LOGISTIC REGRESSION AND PREDICTION OF COMPLICATIONS COMPARING ALL CASES WITH THE 44 CASES WHO HAD LOBECTOMY OR PNEUMONECTOMY

A. Prediction equations of postoperative complications by preoperative variables for all 57 cases

Variables	Predicted equations	p value
(70%-R)DLCO%	ln (P/ 1-P)=4.105-0.271*(70%-R)DLCO%	<0.001
VO2max/kg	ln (P/1-P)=7.158-0.472*VO2max/kg	<0.01
DLCO% predicted	ln (P/1-P)=14.112-0.198*DLCO% predicted	<0.01
FEV1% predicted	ln (P/1-P)=3.932-0.0575*FEV1% predicted	<0.01

P: the probability of developing complication.

B. Prediction equations of postoperative complications by preoperative variables for the 44 cases who had lobectomy or pneumonectomy

Variables	Predicted equations	p value
(70%-R)DLCO%	ln (P/ 1-P)=8.022-0.394*(70%-R)DLCO%	<0.001
VO2max/kg	ln (P/1-P)=6.709-0.426*VO2max/kg	<0.01
DLCO% predicted	ln (P/1-P)=12.873-0.176*DLCO% predicted	<0.01
FEV1% predicted	ln (P/1-P)=4.091-0.0555*FEV1% predicted	<0.01

P: the probability of developing complication.