**MECHANISMS OF EXERTIONAL DYSPNEA IN POSTSURGICAL PATIENTS WITH NON-
SMALL CELL LUNG CANCER**

by

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Abstract

Background: Dyspnea is a debilitating symptom reported by patients with non-small cell lung cancer (NSCLC) after pulmonary resection. Reduced ventilatory capacity and respiratory muscle weakness associated with surgery could lead to an imbalance between ventilatory effort and output (a phenomenon known as neuromechanical uncoupling [NMU]) and result in dyspnea. Additionally, augmented pulmonary vascular resistance may impair left ventricular (LV) stroke volume (SV), and contribute to dyspnea and exercise intolerance. It was therefore hypothesized that greater NMU would be associated with dyspnea and exercise intolerance in NSCLC. It was also hypothesized that reduced diastolic filling and decreased LV SV would be associated with dyspnea and exercise intolerance in NSCLC.

Methods: Using a cross-sectional design, thirteen post-surgical NSCLC patients performed a pulmonary function test and an incremental cardiopulmonary exercise test, followed by constant-load cycling exercise at 25%, 50%, and 75% W_{max} . At 75% W_{max} , patients exercised until symptom limitation. The sensory intensity, unpleasantness and sensory qualities of dyspnea were measured during exercise using the modified Borg scale and the multidimensional dyspnea profile. Ventilatory parameters, esophageal pressures, and operational lung volumes were measured continuously; echocardiography was employed during the constant-load trials. Healthy, sedentary age and sex-matched individuals were selected from our database for comparison to the NSCLC group.

Results: Patients with NSCLC reported greater intensity of dyspnea for a given power output when compared to controls, particularly during higher intensity exercise. NMU was unchanged throughout exercise despite significant reductions in ventilatory capacity ($p < 0.05$). There was a significant correlation between the resting E/A and exercise tolerance ($r^2 = 0.58$; $p = 0.035$); however, there were no significant correlations observed between ventilatory or cardiovascular parameters and dyspnea or exercise tolerance.

Conclusion: In contrast to our hypothesis, we observed no evidence of NMU during exercise in NSCLC. The lack of association between ventilatory parameters and dyspnea suggests that the mechanisms of dyspnea are different from those previously identified in other respiratory diseases.

The primary constraint to exercise appeared to be ventilatory limitation secondary to reduced ventilatory capacity and increased ventilatory demand due to peripheral deconditioning. Therapeutic interventions that improve aerobic capacity and reduce ventilatory drive are now warranted with the ultimate aim of reducing dyspnea in this population.

Preface

Chapter 2 is based on work conducted at the Kelowna General Hospital by Ms. Megan Harper, Dr. Neil Eves, and Dr. Michael Humer. The study idea was conceived by Ms. Megan Harper, Dr. Neil Eves, and Dr. Michael Humer. Ms. Megan Harper was responsible for recruitment of all study participants, conducting all testing sessions, data analysis and interpretation, and writing and editing of the thesis. Dr. Neil Eves was responsible for overseeing all aspects of the study. He supervised exercise testing and contributed to data interpretation and editing of the thesis. Dr. Michael Humer assisted with patient recruitment. Ms. Jinelle Gelinas assisted with exercise testing. Ethics approval was obtained from both the Interior Health Ethics Board (2014-15-017-H) and the University of British Columbia (CREB Number H14-01718). Certificates obtained are presented in Appendix B.

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List of Abbreviations

NSCLC	Non-small cell lung cancer
FEV ₁	Forced expiratory volume in one second
FVC	Forced vital capacity
TLC	Total lung capacity
FRC	Functional residual capacity
RV	Residual volume
VO ₂	Oxygen consumption
CPET	Cardiopulmonary exercise test
CLT	Constant-load trial
EILV	End-inspiratory lung volume
EELV	End-expiratory lung volume
IRV	Inspiratory reserve volume
SI	Sensory intensity
A1	Unpleasantness
BSA	Body surface area
EDV	End-diastolic volume
EDVI	End-diastolic volume index
ESV	End-systolic volume
ESVI	End-systolic volume index
SV	Stroke volume
SI	Stroke index
Q	Cardiac output
CI	Cardiac index

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Chapter 1 Review of Literature

1.1 Prevalence and Burden of Lung Cancer

Lung cancer is the most prevalent cancer worldwide [1]. Global incidence rates continue to increase, with an estimated 1.8 million new cases in 2012. It is the most common cancer in men, accounting for more than 1 in 10 of all cancers. In women, incidence rates remain lower and the prevalence of breast cancer still exceeds that of lung cancer. However, the disparity in global incidence rates between men and women appears to be narrowing. Almost half of all Canadians will develop cancer in their lifetime [2]. In 2015, lung cancer is expected to account for nearly 14% of all new cancer cases, remaining the second and third most common cancer in Canadian women and men, respectively [2, 3].

Trachea, bronchus, and lung cancers are the fifth leading cause of death worldwide and were responsible for 1.6 million deaths in 2012, largely driven by deaths in upper-middle and high income countries [1]. Furthermore, lung cancer is the leading cause of cancer-related deaths in both men and women. Cancer remains the leading cause of death in Canada, with 1 in 4 Canadians expected to die from cancer [2]. In Canada, lung cancer results in more cancer-related deaths than the other three major cancer types combined (i.e. breast, colorectal, and prostate cancer) [2].

The incidence and mortality rates of lung cancer in Canada continue to be higher in men compared to women; however, rates have been converging since 1988 as a result of historical differences in tobacco use [2, 3]. Tobacco use among men began to decline in the mid-1960s, following the first federal reports linking tobacco smoking to specific diseases including lung cancer [2]. The significance of reductions in tobacco use among men became evident in the mid-1980s when lung cancer incidence and mortality rates originally began to decline [2]. In contrast, females did not reduce tobacco use until the mid-1980s and incidence and mortality rates only began to stabilize in females in the period between 2001 and 2010, with declines expected in the next two decades [2].

Despite promising results following smoking cessation efforts, the average annual number of new cancer cases in Canada is estimated to increase 79% over the next two decades [2]. This is the combined result of the aging population, with the proportion of Canadians aged 65 years and older increasing from 1 in 8 to 1 in 4, and an estimated 30% increase in the total population during this period [2].

The changing Canadian population will increase the already substantial economic burden of cancer. In 2008, cancer was ranked the 7th mostly costly illness as reported by the Public Health Agency of Canada [2]. The cost of cancer was estimated to be \$4.4 billion in direct and indirect health care costs [2]. Indirect costs included those associated with lost productivity due to illness or premature death; cancer presented the greatest financial burden associated with lost productivity due to premature death of all illnesses included in the analysis [2]. Furthermore, the costs associated with treating cancer are increasing due primarily to increased use of adjuvant therapy, post-treatment home care, and increasing expenditures for cancer-related surgeries [4]. The total cost of treatment, screening, and adjunct smoking cessation programs is projected to be over \$600 million in 2015, rising to more than \$830 million by 2030 [2]. Costs associated with the treatment of lung cancer throughout Ontario increased by approximately 50% from 1997 to 2007, due largely to advancements in surgical techniques [4]. These figures highlight the importance of prevention efforts to reduce cancer-related expenditures, which consume a growing share of limited health care budgets [4].

1.2 Definition, Diagnosis and Treatment of Non-Small Cell Lung Cancer

Of the 26,600 expected new cases of lung cancer in Canada in 2015, 85 to 90% of these will be non-small cell lung cancer (NSCLC) [2, 5]. The remaining 10 to 15% of cases will be small cell lung cancer, the most aggressive form of lung cancer [5]. Small cell lung cancer is characterized by undifferentiated tumors that tend to originate in the bronchi near the centre of the lungs [5]. As a result of its aggressive nature, distant metastases are often present at the time of diagnosis [5]. Consequently, the primary treatment for small cell lung cancer is chemotherapy [5]. Radiation therapy

may be used in combination with chemotherapy in the case of limited stage small cell lung cancer, in which cancer is located within only one side of the chest or the mediastinum [5]. Small cell lung cancer is considered to be extensive when it has spread to the other side of the chest or to other areas of the body [5]. The median survival time for limited versus extensive small cell lung cancer is 16 to 24 months and 6 to 12 months, respectively [5].

There are three main types of NSCLC: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [5]. Adenocarcinoma forms in the glandular cells (type II pneumocytes) on the periphery of the lung [5]. It accounts for 40% of cases and is the most common type of NSCLC [5]. Adenocarcinoma is primarily found in current or former smokers, however, it is also the most common histology found in non-smokers, females, and younger individuals. Approximately 25 to 30% of NSCLC cases are squamous cell carcinomas. Squamous cell carcinoma forms in the squamous cells that line the bronchi and most commonly originates in the large bronchi near the hilum of the lung. In comparison to adenocarcinoma, squamous cell carcinoma is more likely to metastasize later in the disease course. Large cell carcinoma is the least common of the three main types of NSCLC, occurring in 10 to 15% of cases. Large cell carcinoma can occur in any part of the lung and is characterized by undifferentiated cells that lack definite glandular or squamous morphology. It can be described as a diagnosis of exclusion, and has been more recently classified as NSCLC not otherwise specified (NSCLC-NOS) [6].

Lung carcinogenesis requires the accumulation of multiple genetic and epigenetic alterations. These include specific chromosomal alterations or deletions, and gene amplification [7]. For example, the known tumor suppressor gene p53 is estimated to be inactivated in up to 80% of NSCLC cases [7]. The transcription factor p53 is a sequence-specific DNA-binding factor responsible for activating genes involved in cell cycle progression and the regulation of apoptosis, or programmed cell death. Inactivation of tumor suppressor genes, including p53, impairs the regulation of cell cycle progression, leaves DNA unrepaired, and prevents apoptosis, thereby increasing susceptibility to further mutations [7].

Tumor formation also involves the mutation or amplification of oncogenes. Some of the most common genes implicated in NSCLC include: the Kirsten rat sarcoma viral oncogene homolog (KRAS) gene, the epidermal growth factor receptor (EGFR) gene, and the anaplastic lymphoma kinase (ALK) gene [8]. The binding of specific ligands to EGFR activates signaling cascades that modulate the transcription of genes involved in cell proliferation and apoptosis [7]. Gene amplification or mutations lead to EGFR overexpression or upregulation, ultimately resulting in uncontrolled cell division [7].

The progression to malignant cells further requires the activation of telomerase, a telomere-lengthening enzyme necessary for prolonged cell survival, and the expression of vascular endothelial growth factor (VEGF) [9]. Overexpression of VEGF by tumor cells stimulates angiogenesis, the formation of new blood vessels from pre-existing vasculature, thus enabling improved tumor blood flow and continued tumor growth and potential metastasis [9].

Developments in our understanding of the pathogenesis of lung cancer have facilitated the identification of risk factors and their role in the etiology of lung cancer. The most important preventable risk factor for lung cancer continues to be smoking tobacco. Cigarette smoking is related to more than 85% of lung cancer cases in Canada [2]. A history of cigarette smoking is associated with a 20-fold increase in lung cancer risk compared to lifetime non-smokers [10]. Despite this, nearly 1 in 5 Canadians continue to smoke, amounting to over 5 million individuals and contributing to the thousands of lung cancer deaths each year [2]. This highlights the importance of smoking cessation efforts, including public awareness, tobacco control legislation, increased taxation, and tobacco dependence treatment. Furthermore, current clinical guidelines recommend interventions that include counseling and pharmacotherapy for high risk individuals or patients undergoing treatment for lung cancer [11].

Additional risk factors for lung cancer include radon, asbestos, ambient air pollution, chronic lung disease (e.g. chronic bronchitis, emphysema), occupational exposure to chemical carcinogens, and personal or family history of lung cancer. Radon exposure is the leading cause of lung cancer in non-smokers, increasing lung cancer risk nearly 4-fold [8]. It is now recognized that the genetic

mutations underlying lung cancer are dependent upon the interrelationship between environmental or occupational exposures and individual susceptibility. This could include inherited genetic susceptibility to lung cancer or its risk factors (e.g. nicotine addiction, chronic lung disease).

The most common clinical feature on presentation of lung cancer is a persistent or worsening cough [12]. Shortness of breath may develop early in the disease course in up to 60% of patients [12]. A similar proportion of patients present with chest pain and blood-stained sputum (hemoptysis) at the time of diagnosis [12]. Additional signs and symptoms of lung cancer include: wheezing, frequent chest infections, weight loss and fatigue [12].

Chest radiography is most frequently the first step in lung cancer diagnosis. Further imaging techniques include the use of computed tomography (CT), positron emission tomography (PET), and combined endoscopic ultrasonography procedures [8]. Cytologic specimens may be obtained for diagnosis from sputum, bronchial brushings, or bronchoalveolar lavage. Biopsy specimens for histologic examination may also be obtained from endobronchial, transbronchial or transthoracic biopsy procedures. Recent developments include the use of endobronchial ultrasound (EBUS) to perform needle aspiration of mediastinal and hilar lymph nodes, in place of mediastinoscopy which requires the use of an incision made in the neck [12]. The distinction of histologic subtypes from biopsy specimens depends on criteria including cell size, nucleoli, nuclear-to-cytoplasmic ratio, cell shape, and identifiable growth patterns.

The pathologic diagnosis of lung cancer continues to develop, with the evolution of molecular testing in lung cancer. An updated classification system for the subtypes of NSCLC has been developed in response to the growing recognition of the therapeutic implications of histologic classification and molecular testing. Furthermore, investigation is ongoing into the role of molecular testing in providing early detection biomarkers and novel targets for chemoprevention in high risk individuals.

The role of chest radiography and sputum cytology in the early detection of lung cancer among high risk individuals was examined in the 1970s; however, screening trials were ineffective in

reducing mortality, despite improving early detection [13]. More recently, a number of large-scale randomized controlled trials have investigated the capacity of low-dose computed tomographic screening to reduce mortality in heavy smokers. The National Lung Screening Trial (NLST) in the United States represents the largest trial comparing low-dose CT and chest radiography conducted to date [14]. The NLST found that annual screenings with low-dose CT resulted in a 20% relative reduction in mortality from lung cancer in comparison to screening with chest radiography [14]. Consequently, annual low-dose CT screening is currently recommended for high risk individuals aged 55 to 74 years, similar to those included in the NLST, pending further information regarding the outcomes of low-dose CT screening. Recommendations include exercising caution in the use of low-dose CT screening due to the difficulties surrounding description of baseline risk, risk from radiation exposure, disparities in test interpretation and the implications of their findings [11].

The staging of NSCLC uses the tumor (T), node (N), metastasis (M) classification system. The TNM system considers the size of the primary tumor and satellite nodules in the ipsilateral non-primary lobe(s), the degree of spread to regional lymph nodes, and the presence of metastases beyond regional lymph nodes. Updates to the classification system are the product of differences in survival rates between individuals, dependent upon tumor size and disease proliferation. Such updates facilitate more precise assessment of prognosis. The TNM system is used to distinguish the four primary stages of NSCLC. The first three stages are further divided into A and B subgroups. In general, prognosis worsens with progression from stages I to IV.

Surgery remains the cornerstone of treatment for stages I-II (early stage) NSCLC but is used less commonly in stage IIIA (locally advanced) NSCLC [15]. Surgical resection may involve a wedge resection or segmentectomy, or the removal of one or more lobes of the lung, termed a lobectomy. The resection of an entire lung, termed a pneumonectomy, may be performed in more advanced disease. The administration of platinum-based adjuvant chemotherapy in patients with stage II-IIIA NSCLC has become more widespread in recent years following substantive evidence of 5-year survival benefits. Further developments include movement towards personalized adjuvant chemotherapy, following recognition of specific genetic mutations that can be treated with targeted

therapy. The role of adjuvant radiotherapy remains unclear after numerous prospective trials have indicated an adverse effect of postoperative radiotherapy on survival. Despite this, the advent of stereotactic body radiotherapy (SBRT), with its capacity to deliver precise high-dose radiation with limited exposure to surrounding tissues, provides an exciting avenue for exploration of its utility in treating early stage NSCLC [16].

In Canada, the 5-year relative survival rate for lung cancer is 17% [2]. However, in patients with early stage NSCLC who are eligible for surgical resection, survival rates are increased nearly 2.5-fold [17]. 5-year survival rates in patients with resectable NSCLC range from 73% for pathological stage IA to 25% for pathological stage IIIA [18]. The growing number of cases of NSCLC and the prevalence of cancer survivors will have an increasingly important impact on the demand for healthcare services and the need for effective patient support and follow-up care [4].

In addition to staging of NSCLC, surgical eligibility is dependent upon the physiologic evaluation of the patient. Measures of cardiovascular risk and pulmonary reserve should be completed when being considered for resectional surgery [11]. In patients with moderate impairment, a cardiopulmonary exercise test (CPET) to measure maximal exercise capacity is indicated [11]. Simple exercise tests including stair climbing, may also be used to estimate maximal exercise capacity to predict post-operative outcome [11]. However, post-operative outcome is largely defined in the literature relative to morbidity and mortality; functional status among postsurgical patients is much less understood.

1.3 Physiological Impact of Pulmonary Resection for NSCLC

Ventilatory capacity is consistently shown to decline following pulmonary resection, as evidenced by reductions in total lung capacity (TLC) and forced vital capacity (FVC) in postoperative patients with NSCLC. Studies investigating pulmonary function in patients with NSCLC more than 3-months after lobectomy or pneumonectomy report average declines in FVC of 10-15% and 35-40%, respectively [19-24]. Similar results are observed for forced expiratory volume in one second (FEV₁);

therefore the ratio of FEV₁/FVC is maintained postoperatively. The degree of pulmonary functional impairment after pulmonary resection is related to the volume of lung parenchyma removed, or the extent of resection, and is also dependent upon the time-point of postoperative assessment [21].

A number of studies have examined the time course of changes in pulmonary function after surgery [19, 21, 22, 24]. A study by Bolliger et al. [21] assessed pulmonary function in patients with NSCLC at 3- and 6-months post-resection. Patients experienced significant declines in FEV₁, FVC, and TLC after 3-months [21]. Pulmonary function remained significantly reduced compared to preoperative values at 6-months in both lobectomy and pneumonectomy patients; however, the lobectomy group demonstrated significant improvements in FEV₁, FVC, and TLC in the period between 3- and 6-months [21]. In contrast, pulmonary function remained unchanged after 3-months in the pneumonectomy group [21]. A similar pattern of results were found in a subsequent study by Nezu et al. [22]; however, Win et al. [24] found no significant improvements in pulmonary function in the period between 3- to 6-months following either lobectomy or pneumonectomy. Win et al. [24] suggested that this discrepancy may have been the result of differing surgical population demographics, specifically, the older mean age and the relatively greater proportion of females included in their sample.

The disproportionate early loss of function observed among patients after lobectomy is thought to be due to thoracic wall injury and restriction following surgery and the resulting postoperative pain [21, 22, 24, 25]. However, this does not explain the relative stability of pulmonary function beyond 3-months after pneumonectomy. Decrements in function during the early postoperative period after either lobectomy or pneumonectomy may also be the result of deconditioning associated with sedentary behavior in the perioperative period. Functional improvements with time in patients after lobectomy may therefore be the result of increased physical activity levels coinciding with repair of the surgical injury to the chest wall and the resulting alleviation of pain. Surgical injury repair and reductions in postoperative pain are thought to be responsible for the early improvements in pulmonary function demonstrated among patients after lobectomy between assessments at 2-weeks and 1-month [25, 26]. In contrast, continued exercise avoidance or early

cessation of exercise among patients after pneumonectomy may be the result of prolonged chest wall pain or the relative severity of symptoms, such as shortness of breath, which follow pulmonary resection.

Static lung volumes after pulmonary resection are commonly augmented in relation to the extent of resection due to hyperinflation of the remaining lung parenchyma [27]. In a study of twelve patients following extensive pulmonary resection, mean values for TLC, functional residual capacity (FRC), and residual volume (RV) were 57%, 57%, and 69% of predicted, respectively [27]. However, the ratios of FRC/TLC and RV/TLC were 104% and 119%, respectively [27]. Dilatation of the remaining alveoli is compensatory in nature and occurs without destruction of the elastic tissue [19]. Hyperinflation causes a shift towards the flat portion of the pressure-volume curve of the lung, which may impair ventilation [19]. Furthermore, the diameter of the capillaries surrounding the alveoli are reduced at large lung volumes due to stretching and subsequent thinning of the alveolar walls, in addition to direct compression from large surrounding alveoli, therefore increasing vascular resistance and the potential for ventilation-perfusion mismatch in the remaining lung tissue [19]. In addition to reductions in dynamic lung compliance, static lung compliance is diminished due to the overall decrease in lung volume with resection [19, 20, 27, 28].

The diffusing capacity of the lungs for carbon monoxide (D_{LCO}) is not significantly reduced after 6-months in patients who have undergone lobectomy [20, 21]. In patients after pneumonectomy, D_{LCO} is significantly reduced at rest; however, it is often high with respect to the extent of resection due to recruitment of the remaining alveolar surface via pulmonary hyperinflation [20, 21, 29]. Consequently, impairments in gas transfer are generally mild and arterial blood gases are maintained at rest after either lobectomy or pneumonectomy [27, 29, 30].

Relatively fewer studies have investigated the hemodynamic effects of pulmonary resection, which traditionally involved invasive hemodynamic measurement via right heart catheterization. The use of Doppler echocardiography to measure pulmonary hemodynamics has become more widespread in recent decades and further enables the examination of changes in cardiac morphology and function after pulmonary resection [31, 32]. Both direct and indirect measurements of pulmonary

artery systolic pressure (PASP) demonstrate significant increases in PASP in patients after pulmonary resection due to reductions in the pulmonary vascular bed [27, 31, 32]. These increases are found to be more pronounced in patients after pneumonectomy in comparison to lobectomy [31, 32]. Similar results were found for mean pulmonary artery pressure (MPAP) in patients after extensive pulmonary resection [20, 27, 33]. Right ventricular pressure overload in patients after pulmonary resection is associated with progressive right ventricular dilation [31, 32]. In a study of fifteen patients who underwent pneumonectomy for NSCLC, progressive increases in right ventricular diastolic diameter (RVDD) developed alongside increases in PASP up to four years after pneumonectomy [31]. Invasive studies of pulmonary hemodynamics suggest that pulmonary vascular resistance (PVR) is maintained within the normal range at rest, despite chronic increases in blood flow per unit of lung [20, 33]. Furthermore, pulmonary capillary wedge pressure (PCWP) is normal at rest and therefore filling pressure appears to be maintained [27, 33]. However, cardiac output is generally considered to be slightly reduced at rest due to reductions in pulmonary blood volume [20, 27, 33].

As pulmonary resection is the mainstay of treatment for early stage NSCLC, the impact of pulmonary resection on health-related quality of life (HRQOL) in NSCLC patients has received considerable attention in the literature in the last decade [34]. The most common symptoms experienced by patients after treatment for NSCLC are pain, fatigue, dyspnea, and cough. Of these, the most prevalent symptom is dyspnea, a sensation of labored or difficult breathing [34-36]. Dyspnea is a frequent and highly debilitating symptom that most often presents with exertion and is associated with increased levels of depression, anxiety, and exercise-avoidance. Over 20% of patients present with dyspnea at the time of diagnosis, however, the incidence of dyspnea has been shown to increase 3-fold after pulmonary resection [37]. Furthermore, dyspnea persists for several years post-surgery and remains elevated compared to preoperative levels [34, 37].

Patients experience significant reductions in exercise tolerance following pulmonary resection, as evidenced by declines in peak oxygen uptake (VO_{2peak}) of 10-15% and 20-30% after lobectomy and pneumonectomy, respectively [20-24]. Measures of pulmonary function such as FEV_1

have traditionally been used to predict declines in exercise tolerance after pulmonary resection; however, impairments in exercise tolerance are disproportionate to changes in pulmonary function, which have been shown to consistently overestimate reductions in $\text{VO}_{2\text{peak}}$ [38]. Declines in exercise tolerance are therefore likely dependent on the combined effects of declines in pulmonary functional reserve and diffusing capacity, and alterations in skeletal muscle and cardiovascular function after pulmonary resection [33]. An improved understanding of the mechanisms of exercise limitation in postsurgical patients with NSCLC is of the utmost importance, as every $1 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ decline in $\text{VO}_{2\text{peak}}$ is related to a 4% increase in all-cause mortality in this population [39].

1.4 Exercise Limitation in NSCLC

A number of studies have investigated the primary factors, which limit exercise tolerance in patients with NSCLC after pulmonary resection. The most consistent finding among the literature is that of a reduction in the ventilatory reserve at peak exercise, expressed as a percentage of maximum ventilatory capacity (MVC), [21, 22, 26, 38]. Ventilatory impairment at peak exercise is more pronounced in patients after pneumonectomy; specifically, ventilatory reserves ($(\text{MVC} - \text{V}_E)/\text{MVC}$) at peak exercise decline to approximately 30% and 20% 6-months after lobectomy and pneumonectomy, respectively [21, 22, 26, 38]. However, only after extensive pulmonary resection were patients found to operate at or near their MVC; this suggests that the majority of patients are not ventilatory limited after pulmonary resection [33].

Patients exhibit a blunted tidal volume response to incremental exercise after pulmonary resection, subsequent to hyperinflation of the remaining lung parenchyma. Patients therefore adopt a more shallow and rapid breathing pattern which, in turn, results in an increased ratio of dead space ventilation to alveolar ventilation [21, 26, 27]. Augmented dead space ventilation and reductions in D_{LCO} are further associated with an increase in ventilation for a given oxygen uptake (VO_2) [40, 41]. The arterial oxygen tension (P_{aO_2}) is reduced at peak exercise in patients after pneumonectomy, but is not found to be significantly reduced after lobectomy [20, 21]. In contrast, the arterial carbon

dioxide tension ($P_a\text{CO}_2$) remains unchanged in comparison to preoperative values in patients after either lobectomy or pneumonectomy, which suggests that alveolar ventilation remains adequate, but that after pneumonectomy, patients may be limited by the diffusion capacity of the reduced alveolar surface [20, 21].

The physiologic reserves of diffusing capacity are recruited even at rest after pulmonary resection, and therefore impose upon exercise reserves [29]. Despite this, the pattern of recruitment of the pulmonary capillary bed during exercise is normal after pneumonectomy and prevents the development of significant diffusion limitation during exercise [29]. Declines in arterial oxygen saturation ($S_a\text{O}_2$) at peak exercise are therefore seen to be mild in patients after pulmonary resection. A study by DeGraff et al. [33] demonstrated that impairments in diffusing capacity do not manifest in significant arterial oxygen desaturation ($S_a\text{O}_2 < 88.5\%$) during exercise until approximately 65% of the lung parenchyma is removed. An examination of the functional significance of reductions in D_{LCO} by Johnson et al. [40], concluded that if normal ventilation and cardiac output are achieved during exercise, diffusing capacity must be reduced to less than 50% of normal before imposing a significant limitation to peak oxygen uptake $\text{VO}_{2\text{peak}}$. In a comparison of eight patients after pneumonectomy to age- and gender-matched healthy controls, D_{LCO} was reduced to 44% of normal at rest in the pneumonectomy group [29]. However, the authors found no evidence to suggest that an upper limit of diffusing capacity was approached during exercise and concluded that a reduced maximal cardiac output imposes the principal limit to exercise tolerance after pulmonary resection [29].

In the seminal investigations of DeGraff et al. [33] and Mossberg et al. [27], invasive measures of cardiac output were collected during submaximal constant load exercise in patients after extensive pulmonary resection. The results of these studies together showed a decline in cardiac output for a given VO_2 compared to normal, which the authors suggested to be the result of a reduced stroke volume due to impaired filling of the left ventricle secondary to a decreased pulmonary blood volume [27, 33]. Furthermore, PVR was noted to exhibit an abnormal response to exercise, whereby PVR failed to decrease and was therefore increased at peak exercise in comparison to normal [27, 33]. Van Mieghem et al. [20] conducted the first study to utilize invasive right heart catheterization to

compare cardiopulmonary function at peak exercise preoperatively and 6-months after lobectomy or pneumonectomy. MPAP tended to be augmented at peak exercise postoperatively in both groups [20]. PVR was significantly increased at peak exercise in patients after pneumonectomy; together with increases in MPAP, augmented PVR was thought to indicate limited reserves in recruitment and distension of the pulmonary capillary bed [20]. Increases in MPAP appeared to parallel those in mean pulmonary capillary wedge pressure (MPCWP), and therefore the pressure gradient across the pulmonary vascular bed was largely maintained throughout exercise [20, 27]. Similar to previous reports, stroke volume and cardiac output were impaired at peak exercise [20, 22, 27, 33]. The mechanism by which the stroke volume response to exercise is impaired is thought to relate to reductions in the pulmonary vascular bed and augmented right ventricular afterload, which may influence left ventricular function via series and/or direct ventricular interaction [20].

The most common reasons for exercise cessation cited by patients after pulmonary resection are dyspnea, or shortness of breath, and leg fatigue [21, 22, 27]. Preoperatively, the majority of patients report leg fatigue to be the principal factor limiting exercise [21, 22, 38]. This trend is sustained in patients after lobectomy and is thought to be secondary to the myopathic effects of cancer cachexia, deconditioning, or drug toxicity related to adjuvant chemotherapy [21, 22, 42]. However, these results are based on cardiopulmonary exercise tests performed on a cycle ergometer and are likely mode dependent (i.e. cycle vs. treadmill), as has been demonstrated in patients with COPD [43]. Inconsistencies in symptom ratings between exercise modes is related to the increased muscle mass, and hence greater oxygen and ventilatory demands, involved in treadmill exercise. Despite this, more than 35% of patients after lobectomy cite dyspnea as the primary reason for exercise cessation, either alone or in combination with leg fatigue [22]. Deconditioning, subsequent to sedentary behavior in the perioperative period, is evidenced by significant impairments in peripheral muscle strength among cancer patients in comparison to healthy controls [42]. Furthermore, peripheral muscle performance was found to be predictive of exercise capacity in patients with lung cancer [44].

No study to date has investigated the influence of pulmonary resection on peripheral muscle strength. A study by Pelletier et al. [38] identified both leg fatigue and dyspnea to be significantly increased for a given workload after either lobectomy or pneumonectomy in the early postoperative period. The most common factor limiting exercise in both groups was therefore a combination of the two symptoms [38]. Conversely, the vast majority of patients after pneumonectomy are limited by dyspnea 3- or 6-months postoperatively [21, 22, 27]. Discrepancies in the subjective factors limiting exercise tolerance after either lobectomy or pneumonectomy appear to be the result of the relative preservation of pulmonary and cardiovascular reserves after lobectomy. Exertional dyspnea in patients after pulmonary resection may also be associated with deconditioning due to earlier metabolic acidosis and ventilatory stimulation, which may contribute to exercise limitation [42]. Increased ventilatory stimulation results in enhanced afferent feedback from multiple sensory systems, including mechanoreceptors in the lungs, airways, and respiratory or peripheral musculature, chemoreceptors, and skeletal muscle metaboreceptors [45]. Afferent feedback is relayed through a variety of neural pathways in an effort to produce the appropriate ventilatory response for a given respiratory motor drive [45]. The role of dyspnea in exercise intolerance is thought to be related to an inability to achieve necessary ventilatory outputs, subsequent to functional impairments associated with cancer and its therapies [45, 46].

1.5 The Sensation of Dyspnea and Its Measurement

Dyspnea has traditionally been described as a subjective experience of breathlessness or breathing discomfort. Such a simplified definition, however, discounts the complex nature of this symptom. Dyspnea is a multidimensional symptom, comprised of qualitatively distinct sensations that have both sensory and affective dimensions which act to govern its intensity and unpleasantness as perceived by the patient [47]. Shortness of breath is the most common cause of emergency department visits among all cardiopulmonary diagnoses [47]. Shortness of breath has a profound negative impact on HRQOL and is an independent predictor of mortality in patients with NSCLC [35, 48]. Dyspnea is associated with increased levels of depression, anxiety, and reduced levels of

physical functioning [37]. The emotional influence of dyspnea undermines self-confidence among patients in being able to perform physical activity, resulting in premature cessation of exercise and exercise avoidance [34, 45]. Such limitations impair the capacity for patients to perform activities of daily living and leads to additional loss of functional independence, which further increases mortality risk [39, 49].

A number of measurement tools have been developed for the purpose of quantifying the experience of breathlessness. Instruments vary in the domain(s) of dyspnea measured, the rating task, and the time-frame for measurement. The suitability of a given measure is dependent upon the specific needs of the clinician(s) or researcher(s) employing the measurement tool. Therefore numerous attempts have been made to categorize dyspnea measures according to the various domains of the symptom a given instrument is designed to address. Recent recommendations propose that instruments should be classified as pertaining to domains of sensory-perceptual experience, affective distress, or symptom impact or burden. Sensory-perceptual evaluations most commonly involve one or more single-item scales (e.g. visual analog, Likert-type, numerical) to assess the intensity or sensory quality of dyspnea. Single- or multiple-item scales relating to the affective dimension of dyspnea are further divided into evaluations of either immediate unpleasantness or emotional distress. Furthermore, a number of questionnaires have been developed to assess the impact or burden of dyspnea in relation to functional status or quality of life. Clinical rating methods include the Baseline Dyspnea Index (BDI), Chronic Respiratory Disease Questionnaire (CRQ), and the Modified Medical Research Council (MRC) Dyspnea Scale. Relatively fewer questionnaires have been validated within the cancer population; however, the Cancer Dyspnea Scale and the Lung Cancer Symptom Scale have been developed to assist in the management of patients with lung cancer. Questionnaires generally involve short-term recall of a specific episode or time interval and further vary in the dimensions of symptom- or disease-impact which they address. These instruments often lack evaluation of the magnitude of intensity, sensory quality or affective dimension of dyspnea. Therefore questionnaires vary in their usefulness in acute laboratory or clinical research settings.

Two of the most prevalent scales used to quantify breathlessness in acute laboratory or clinical research settings are the visual analog scale (VAS) and the Borg scale. The VAS requires dyspnea to be rated along the distance of a vertical or horizontal line commonly 10 cm in length with descriptive phrases anchoring the two extremes of breathlessness at each end [50, 51]. Patients are instructed to mark a point along the scale that corresponds with the perceived intensity of dyspnea. The principle limitation of the VAS is the absence of defined levels or categories to facilitate comparisons between individuals. Borg [52] developed the first category scale to enable direct interindividual comparisons for ratings of perceived exertion (RPE) during an incremental exercise test. Borg later modified the scale to develop a 12-point category scale with ratio properties suitable for measuring subjective symptoms including shortness of breath (CR-10 scale) [53]. The modified Borg scale is a vertical scale labeled 0 to 10 anchored by simple verbal descriptors. Subjects are permitted to use decimals and to provide ratings beyond the identified range in order to prevent a ceiling effect. The VAS and the modified Borg scale are the two most commonly used instruments for evaluating dyspnea during exercise [50]. Ratings of breathlessness obtained during exercise with the Borg scale have been shown to be highly reproducible and to have a similar coefficient of variation to physiologic measures of intensity. Both the VAS and the modified Borg scale have been shown to be valid and reliable tools for use in healthy subjects and in patients with chronic respiratory disease in either the laboratory or clinical (emergency department) settings [53-56]. However, the modified Borg scale is shown to have superior reliability and to correlate more closely with cardiopulmonary and metabolic parameters during exercise [54, 55]. Moreover, it provides immediate feedback in response to changing stimuli. Its utility during exercise has led to its widespread use in studies examining the mechanisms that underlie breathlessness especially in patients with respiratory disease.

An appreciation for the distinct qualities of dyspnea and the relevance of their measurement has developed over the past three decades. Simon et al. [57] conducted the first study to discern the various qualities of dyspnea and to test the hypothesis that distinct sensations of breathlessness are evoked in response to different respiratory stimuli. This led to the characterization of three primary sensations that contribute to dyspnea: 'air hunger' or 'unsatisfied inspiration', 'work/effort', and 'tightness'. It has also more recently been proposed that similar to pain, the sensory intensity and

unpleasantness of dyspnea are discrete dimensions that can be objectively evaluated [58-60]. Specifically, the sensation of air hunger is found to be notably more unpleasant and to evoke more anxiety, frustration, and fear than the perception of maximal respiratory work [58]. It is therefore concluded that there are multiple sensory dimensions of dyspnea that are independent of one another, that may be perceived differently between individuals, and which also appear to vary in the physiological processes that govern them.

The need for a measurement tool that would encompass the complexities of dyspnea and therefore improve upon existing instruments designed primarily to evaluate the severity or intensity of dyspnea, developed along with increasing awareness of the multidimensional nature of dyspnea. The Multidimensional Dyspnea Profile (MDP) was developed by Banzett et al. [61] to provide a comprehensive assessment of the immediate unpleasantness, sensory quality, and emotional response related to dyspnea. The MDP has been shown to be a valid and reliable measurement tool with utility in responding to changes in either laboratory-induced or clinical sensations of dyspnea [61].

1.6 Mechanisms of Dyspnea

The maintenance of adequate alveolar ventilation requires the coordinated response of the respiratory center in the medulla to afferent feedback from a variety of receptors that detect stretch, tension, irritation, metabolites, and pressure in the respiratory, cardiovascular, and musculoskeletal systems [45]. Dyspnea is associated with abnormalities in the mechanisms that regulate normal respiration and is most often associated with conditions in which (1) central motor output is increased or (2) the system is subject to a mechanical load [62]. The qualities of dyspnea are modified by the varying stimuli and their respective afferent pathways [45].

The sense of respiratory effort is related to the pressure generated by the respiratory muscles in relation to their maximum pressure generating capacity [62]. The pressure generated by the respiratory muscles during inspiration is measured using esophageal pressure (P_{es}), a surrogate for

pleural pressure. Respiratory effort is therefore quantified using the ratio of P_{es} to the maximum inspiratory pressure generating capacity (P_{IMax}) [36]. This index of respiratory effort has been shown to be strongly associated with ratings of dyspnea in patients with chronic obstructive pulmonary disease (COPD), however, it has yet to be explored in cancer populations [36]. With increasing ventilatory demands during exercise, patients with COPD experience mechanical constraints on tidal volume expansion subsequent to increasing dynamic hyperinflation. As end-inspiratory lung volumes continue to increase and approach total lung capacity, patients become mechanically constrained and the ratio of tidal volume to vital capacity is reduced. Resistive loading of the inspiratory muscles forces patients to operate more closely to their P_{IMax} (P_{es}/P_{IMax}). O'Donnell et al. [36] found ratings of exertional dyspnea to be more strongly related to the ratio of respiratory effort (P_{es}/P_{IMax}) to ventilatory output, measured by tidal volume expressed as a percentage of vital capacity (V_T/VC). Therefore, while dyspnea is dependent upon the magnitude of respiratory effort, the intensity of dyspnea is also mediated by the appropriateness of the ventilatory output for a given effort. Interference in the function of the respiratory system results in increased afferent feedback from multiple sensory systems, including mechanoreceptors in the lungs, airways, and respiratory or peripheral musculature, chemoreceptors, and skeletal muscle metaboreceptors [45]. Afferent feedback is relayed through a variety of neural pathways and results in augmented respiratory motor drive. Sensory information related to the mismatch between the prevailing respiratory motor drive and the resulting ventilatory output, termed neuromechanical uncoupling, activates cortico-limbic structures associated with dyspnea [45, 47].

Some of the earliest enquiries into the factors associated with dyspnea in advanced cancer patients were performed by Dudgeon et al. [63]. Preliminary investigations included a sample of 100 dyspneic cancer patients, of which 49% had primary lung cancer. Of note, was that the authors observed profound abnormalities in MIP, with a median MIP of -16 cm H₂O among the patient group. Impairments in pressure generating capacity are likely to be the result of respiratory muscle deconditioning or muscular atrophy. Patients may experience myopathic changes in peripheral and respiratory musculature secondary to the effects of cancer cachexia, deconditioning, or drug toxicity [42].

In an effort to build upon their previous work, Dudgeon et al. [64] set out to identify the factors contributing to the marked respiratory muscle weakness identified in cancer patients. In an effort to examine the length-tension relationship of the diaphragm, diaphragmatic excursion was quantified using ultrasonography as the displacement of the dome of the diaphragm throughout an inspiratory capacity maneuver (i.e. from the end of a normal expiration to end of a maximal inspiration). Diaphragmatic excursion was found to correlate significantly with MIP; however, diaphragmatic excursion only accounted for 16% of the variance in MIP, which suggests that reductions in MIP may also be due to atrophy of or myopathic changes in the intercostal or accessory muscles of respiration. Of note, is that the median MIP among patients in this follow-up study was -55 cm H₂O, indicating only mild respiratory muscle weakness [64]. This is in contrast to the profound abnormalities in MIP observed previously [63]. The discrepancy between these results are likely due to inconsistencies in disease stage between the two samples, as patients in the subsequent study were outpatients with relatively early-stage disease and/or variation in the distribution of primary cancer diagnoses within each sample.

Despite evidence implicating respiratory muscle weakness in the pathophysiology of cancer, MIP was not found to be significantly associated with the intensity of dyspnea in either study [63, 64]. In contrast, in a sample of 135 terminally ill cancer patients (of which the lung was the primary tumor site in 26% of patients), Bruera et al. [65] found MIP to be an independent predictor of dyspnea intensity in patients suffering from moderate to severe dyspnea. The median MIP among dyspneic patients in their sample was -54 cm H₂O, being similar to that measured by Dudgeon et al. [64] in cancer outpatients. Ratings of dyspnea intensity on a 100-mm visual analogue scale were also similar between the study by Dudgeon et al. [64] and Bruera et al. [65], with median values of 57 mm and 50 mm, respectively. The reasons for such disparity in the association between MIP and dyspnea intensity remain unclear, but differences in the age of the two cohorts, the proportion of men versus women, disease stage, previous treatment, underlying comorbidities, or the distribution of primary cancer diagnoses between the samples may all play a role.

The results of these studies together suggest that respiratory muscle weakness contributes to dyspnea at rest in cancer patients. However, sensations of dyspnea become considerably greater with exertion [42, 45] and it is unknown whether respiratory muscle weakness, changes in lung mechanics, increased ventilatory demand or cardiovascular factors contribute to these adverse sensations. Dyspnea is a multidimensional symptom and there is likely to be a multitude of factors which contribute to the overall sensation of dyspnea, which may depend on the primary site of cancer, therapies received, age, sex, fitness level, or underlying comorbidities.

1.7 Mechanisms of Dyspnea during Exercise in Patients with Cancer

To date, the only study to explore the mechanisms of exertional dyspnea in patients with cancer observed ventilatory pattern abnormalities consistent with dynamic respiratory muscle weakness [42]. Patients with chronic exertional dyspnea presented with a more rapid and shallow breathing pattern during exercise compared to both non-dyspneic cancer patients and healthy controls. Mean values for MIP were normal in all patient groups, however, MIP tended to be lower in the cancer dyspnea group and was correlated with reduced inspiratory capacity and, in turn, with tidal volume restriction throughout exercise. The authors found no evidence for airway obstruction or restrictive interstitial lung disease, which may have otherwise augmented mechanical loading. In light of this, respiratory muscle weakness was suggested to be the primary mechanism of exertional dyspnea in cancer patients. While this study provided preliminary insight into the mechanisms of exertional dyspnea in a general cancer population, patients with lung cancer were excluded from the study, so the mechanisms of exertional dyspnea in lung cancer patients remain unexplored.

Dyspnea results from the interaction between various stimuli and afferent pathways, producing qualitatively distinct sensations. Consequently, the qualitative features of dyspnea differ across diseases [45]. It may therefore be beneficial to study a more homogeneous patient group, as the mechanisms of exertional dyspnea may vary depending on cancer type, disease stage, previous treatments, or underlying comorbidities. Understanding the factors contributing to dyspnea in lung

cancer patients is paramount, as dyspnea remains more prevalent in lung cancer than in any other cancer [65, 66]. Moreover, as the number of people living with or beyond a cancer diagnosis continues to increase, so too does the importance of maintaining HRQOL in these individuals. An improved understanding of the mechanisms responsible for dyspnea in NSCLC will therefore help to enable the development of therapeutic interventions, with the ultimate aim of reducing dyspnea and improving HRQOL in this population.

1.8 Potential Mechanisms of Exertional Dyspnea in Patients with NSCLC

Dyspnea is associated with three primary ventilatory abnormalities: (1) increased work of breathing to overcome a mechanical load, (2) enhanced ventilatory drive, and (3) increased proportion of respiratory muscle strength required to maintain any given ventilation [67]. Patients with lung cancer may be subject to increases in elastic or resistive loading as a result of airway obstruction (commonly secondary to other smoking related disorders) or decreased lung compliance (secondary to radiation-induced fibrosis). Abnormalities in pulmonary function are evidenced by decreases in FEV₁, FVC, FEV₁/FVC, and by obstructive, restrictive, or mixed airflow patterns present on spirometric assessment [63-65]. Ventilatory drive is increased with exercise and may be exaggerated in lung cancer patients due to ventilation-perfusion abnormalities, gas exchange abnormalities, or skeletal muscle deconditioning leading to earlier metabolic acidosis and ventilatory stimulation [42]. Furthermore, evidence suggests that respiratory muscle weakness contributes to dyspnea in patients with lung cancer [63-65]. Such limitations could lead to a potential imbalance between ventilatory effort and ventilatory output, a phenomenon known as neuromechanical uncoupling, which may cause exertional dyspnea in this population [36, 42].

Neuromechanical uncoupling is a well-documented mechanism of exertional dyspnea in patients with COPD [36, 68, 69]. In patients with COPD, dynamic hyperinflation increases tidal breathing towards total lung capacity, resulting in mechanical constraints on tidal volume expansion. This leads to a restrictive ventilatory pattern and an increased work of breathing due to reductions in

lung compliance and an inspiratory threshold load (intrinsic positive end-expiratory pressure) [69]. These abnormalities in pulmonary function result in increased afferent feedback from multiple sensory systems, including mechanoreceptors in the lungs, airways, and respiratory or peripheral musculature, chemoreceptors, and skeletal muscle metaboreceptors [45]. In response, the respiratory center increases efferent motor output to the respiratory muscles, in an effort to augment ventilatory output. Sensations of dyspnea result when the tidal volume response of the respiratory system is inappropriate for the existing ventilatory drive (either due to increased work of breathing or impaired respiratory muscle function) [70]. In patients with COPD, ratings of dyspnea intensity increase throughout exercise in direct proportion to the increasing disparity between ventilatory effort and ventilatory output [68].

After pulmonary resection, patients experience augmented ventilatory stimulation during exercise as a result of peripheral and respiratory muscle deconditioning [42]. Resulting increases in efferent activation may act in combination with respiratory muscle dysfunction to force patients to operate closer to their maximal pressure generating capacity (P_{Imax}) [63-65]. Reductions in ventilatory capacity after pulmonary resection may lead to an inadequate ventilatory response and therefore result in uncoupling of ventilatory effort from ventilatory output. It has also been proposed that static lung compliance is reduced secondary to pulmonary resection and that dynamic lung compliance may be impaired due to hyperinflation of the remaining lung parenchyma [19, 20, 27, 28]. Such limitations may increase the work of breathing and further augment ventilatory stimulation. Therefore, a key contributing factor in patients after pulmonary resection may not be the maximum pressure generating capacity of the muscles, but instead the proportion of pressure generated by the respiratory muscles relative to their maximum, and the coupling of a given respiratory effort to the ventilatory response.

In addition to the changes in pulmonary function in patients with NSCLC, these patients also experience increased PASP after pulmonary resection due to reductions in the pulmonary vascular bed [27, 31, 32]. Progressive increases in right ventricular diastolic diameter have been shown to develop alongside increases in PASP in these patients [31]. The degree of change in PASP is related

to the extent of resection [31, 32]; and while increases in PASP are smaller than those seen in primary pulmonary arterial hypertension (PAH), increased right ventricular afterload may lead to dyspnea in patients with NSCLC similar to what has been shown previously in patients with primary PAH [71]. Reductions in right ventricular ejection fraction and hence right ventricular stroke volume due to increased pulmonary vascular resistance secondary to pressure-overload may lead to impaired left ventricular diastolic filling and reduced stroke volume via series interaction. This may be further exacerbated during exercise in patients with NSCLC due to limited reserves in recruitment and distension of the pulmonary capillary bed after pulmonary resection [20]. Furthermore, diastolic dysfunction is a well-established mechanism of dyspnea in patients with congestive heart failure and may also contribute to dyspnea and exercise intolerance in patients with NSCLC [72].

While the mechanisms of dyspnea are likely multifaceted, there may be common physiological abnormalities consequent of NSCLC and anticancer therapies which lead to exertional dyspnea in this population. Therefore, the primary objective of this pilot study was to explore the potential mechanisms of exertional dyspnea in postsurgical patients with NSCLC.

1.9 Primary Aim

The primary aim of the study was to explore the major factors contributing to exertional dyspnea in NSCLC and to determine the role of dyspnea in exercise intolerance.

1.10 Primary Hypothesis

It was hypothesized that greater neuromechanical uncoupling would be the principal mechanism of dyspnea and that neuromechanical uncoupling would be associated with exercise intolerance in NSCLC.

1.11 Secondary Aim

The secondary aim of the study was to investigate whether the cardiovascular system contributes to dyspnea and exercise intolerance in NSCLC.

1.12 Secondary Hypothesis

It was hypothesized that reduced diastolic filling and decreased left ventricular stroke volume would be associated with dyspnea and exercise intolerance in NSCLC.

Chapter 2 Mechanisms of Exertional Dyspnea in Postsurgical Patients with Non-Small Cell Lung Cancer

2.1 Introduction

Dyspnea has a profound negative effect on health-related quality of life (HRQOL) [34, 35] and is a significant predictor of mortality in patients with non-small cell lung cancer (NSCLC) [48]. Dyspnea is also associated with increased levels of depression, anxiety and reduced levels of physical functioning [37]. Such limitations impair the capacity for patients to perform activities of daily living and lead to additional loss of functional independence, which further increases mortality risk [49]. Alterations to the respiratory, cardiovascular, and/or musculoskeletal systems, subsequent to NSCLC and its therapies, may all increase dyspnea but the precise mechanisms are unknown.

Dyspnea is a multidimensional symptom, comprised of distinct sensations which act to govern its intensity and unpleasantness as perceived by the patient [47]. Debilitating dyspnea can occur with exertion as metabolic and ventilatory demands increase. These demands are increased further following lung resection as a result of reduced lung capacity and skeletal muscle deconditioning. Furthermore, evidence suggests that respiratory muscle weakness contributes to dyspnea in patients with NSCLC [63, 65]. Such limitations could lead to a potential imbalance between ventilatory effort and ventilatory output, a phenomenon known as neuromechanical uncoupling (NMU), which may cause exertional dyspnea in this population. However, these mechanisms remain unexplored in patients with NSCLC.

There is strong evidence that pulmonary artery systolic pressure (PASP) is significantly increased in patients with NSCLC after pulmonary resection due to reductions to in the pulmonary vascular bed [27, 31, 32]. While increases in PASP are less than those seen in primary pulmonary arterial hypertension (PAH), increased right ventricular afterload may lead to dyspnea in patients with NSCLC similar to what has been shown previously in patients with primary PAH [71]. Furthermore,

progressive increases in right ventricular diastolic diameter have been shown to develop alongside increases in PASP in patients with NSCLC [31]. Diastolic dysfunction is a well-established mechanism of dyspnea in patients with congestive heart failure and may therefore also contribute to dyspnea and exercise intolerance in patients with NSCLC [72].

Dyspnea is among the most common and debilitating symptoms in patients with NSCLC, persisting for several years after lung resection [34, 37]. Furthermore, dyspnea leads to exercise avoidance, resulting in further deconditioning and reductions in peak oxygen consumption, an independent predictor of mortality [39]. An improved understanding of the mechanisms responsible for dyspnea in NSCLC will help to enable the development of therapeutic interventions, with the ultimate aim of reducing dyspnea and improving HRQOL in this greatly understudied population. Therefore, the primary objective of this study was to identify the major factors contributing to exertional dyspnea in patients with NSCLC and to determine the role of dyspnea in exercise intolerance. It was hypothesized that greater neuromechanical uncoupling would be the principal mechanism of dyspnea and that neuromechanical uncoupling would be associated with exercise intolerance in NSCLC. The secondary objective was to investigate whether the compromise in cardiac performance contributes to dyspnea and exercise intolerance in NSCLC. It was hypothesized that reduced diastolic filling and decreased left ventricular stroke volume would be associated with dyspnea and exercise intolerance in NSCLC.

2.2 Methodology

2.2.1 Participants

Patients who were >3-months post-surgery for NSCLC and who were stable (i.e. had not had a change in their condition or been admitted to the hospital in the last 6 weeks) were recruited. Patients with cardiovascular contraindications to exercise, exertional hypoxemia ($S_pO_2 < 85\%$), uncontrolled systemic hypertension, musculoskeletal limitations to cycle exercise (e.g. knee pain, leg

pain, osteoarthritis), diabetes, BMI > 35 kg/m² and those unable to understand and sign the consent for participation in the study were excluded. Nine healthy, sedentary individuals matched for age and sex were also selected from our laboratory database to enable comparison of patients with NSCLC to healthy individuals from the same community. These individuals had completed an incremental cardiopulmonary exercise test (CPET) and discontinuous constant-load exercise trials at 25%, 50%, and 75% of the maximum workload (W_{max}) achieved in the CPET. Echocardiographic images were obtained at steady state during the constant-load trials. However, measurements of esophageal pressure were not obtained in either test and patients had not performed an exercise tolerance test.

Patients were recruited from the Kelowna Thoracic Clinic at the Kelowna General Hospital. A poster inviting patients to participate in the study was hung in the waiting area of the clinic and consent to contact letters were available in the waiting area that asked patients to sign the letter if they would like to be contacted with more information about the study. Potentially eligible patients were also informed of the study by the thoracic surgeons or nurse practitioner at their clinic visit and were informed that consent to contact letters were available in the waiting area if they were interested in receiving more information. Letters were collected weekly by Ms. Harper.

Ms. Harper was also available to discuss the study with patients who expressed interest in the study during post-surgical follow-up clinics in the Kelowna Thoracic Clinic. Potentially eligible patients were informed of the study by the thoracic surgeons or nurse practitioner at their clinic visit and were informed that Ms. Harper was available in the clinic to discuss the study should they be interested. Patients who expressed interest in the study had the opportunity to discuss the study with Ms. Harper and were asked to complete a consent to contact letter if they were potentially interested in participating and wished to be contacted with further information.

2.2.2 Study Design

The study was performed using a prospective cross-sectional design with patients coming to the pulmonary function laboratory at the Kelowna General Hospital on one occasion. During this visit,

patients initially performed a pulmonary function test. Following the pulmonary function test, a balloon-tipped catheter was inserted via the nose for the measurement of esophageal pressure. Patients then performed an incremental cardiopulmonary exercise test (CPET) to symptom limitation on an electronically braked cycle ergometer to identify any cardiovascular contraindications to exercise and to provide appropriate exercise intensities for the discontinuous constant load exercise trials. After one hour of rest, patients exercised using a discontinuous protocol at 25%, 50%, and 75% of the maximum workload ($W_{\max}$) achieved in the CPET, with ~10 minutes of rest between each workload. At 75% $W_{\max}$ patients were asked to exercise as long as possible until terminating exercise due to symptom limitation. Echocardiography was performed following obtainment of a steady state at each workload and every 3 minutes at 75% $W_{\max}$ as patients exercised to symptom limitation to assess left ventricular diastolic and systolic function during exercise.

2.2.3 Outcome Variables

The primary outcome was the association between neuromechanical uncoupling (defined [36] as the ratio between tidal inspiratory esophageal pressure [P_{insp}] expressed relative to maximum inspiratory pressure [P_{imax}] and tidal volume [V_T] expressed relative to vital capacity [VC] i.e. $P_{\text{insp}}/P_{\text{imax}} : V_T/VC$) and the intensity of exertional dyspnea. Secondary outcomes included the relationships between left ventricular end-diastolic volume and stroke volume at an isotime during the constant-load trials. Other secondary outcomes included the relationships between all other ventilatory parameters (i.e. ventilation, tidal volume, respiratory rate and operating lung volumes) and changes in inspiratory intrathoracic pressure, oxyhemoglobin saturation, left ventricular end-diastolic volume, and stroke volume and ratings of dyspnea during exercise. When active expiratory muscle work is performed during exercise, neural recruitment of both inspiratory and expiratory muscles occurs to generate pressure throughout the respiratory cycle. As such, we also performed a modified calculation of neuromechanical uncoupling (mNMU) utilizing the swing in esophageal pressure expressed relative to the maximal inspiratory and expiratory (P_{exp}) esophageal pressure swing that could be generated. Such that mNMU was defined as: $P_{\text{exp-insp}}/(\text{maximal expiratory pressure [MEP]} -$

maximal inspiratory pressure [MIP]) : V_T/VC . We also examined selected correlations between measures of exertional dyspnea, ventilatory parameters, left ventricular end-diastolic volume, and stroke volume and exercise tolerance.

2.2.4 Specific Methodology

2.2.4.1 Pulmonary Function Measurements

Routine spirometry and single-breath diffusion capacity for carbon monoxide (D_{LCO}) were measured in the sitting position according to American Thoracic Society (ATS) guidelines [73]. Lung volumes were determined using a constant-volume body plethysmograph (6200 Autobox, SensorMedics, Yorba Linda, CA). Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were measured at FRC and TLC, respectively, using the pressure manometer in the plethysmograph.

2.2.4.2 Cardiopulmonary Exercise Test

An incremental cycle exercise test to symptom limitation was performed in accordance with current ATS/American College of Chest Physicians (ACCP) recommendations [74]. Exercise tests were performed on an electronically braked cycle ergometer (ErgoSelect 200, Ergoline, Bitz, Germany). Patients breathed through a mouthpiece attached to a low-resistance flow transducer (pneumotachograph), while occluding the nasal passages with a nose clip. Resting data were collected for 3 minutes while the patient sat quietly on the cycle ergometer. Patients then completed a one minute unloaded warm-up before entering the $10 \text{ W} \cdot \text{min}^{-1}$ exercise protocol. Patients were asked to cycle between 60-70 rpm throughout the exercise test. Expired gases were analyzed at rest and throughout exercise using a calibrated metabolic measurement system (SensorMedics Vmax 29C, SensorMedics, Yorba Linda, CA). Esophageal pressure (balloon catheter), heart rate (12-lead electrocardiography [ECG]), and oxyhemoglobin saturation (pulse oximetry) were measured

continuously at rest and during exercise. Blood pressure (manual sphygmomanometry), dyspnea (modified Borg scale) and leg discomfort (modified Borg scale) were measured at rest and every two minutes during exercise. Inspiratory capacity maneuvers were also performed at rest, every two minutes during exercise, and immediately prior to exercise cessation to estimate changes in end-expiratory lung volume (EELV). Immediately following exercise cessation, participants were asked to identify which symptom was responsible for exercise cessation (i.e. dyspnea or leg discomfort).

2.2.4.3 Discontinuous Constant Load Exercise Trials

Patients completed a discontinuous exercise trial at 25%, 50%, and 75% W_{max} . Patients were required to cycle for between 3-6 minutes during each exercise trial and were given ~10 minutes of rest between each workload. At 75% W_{max} patients were asked to exercise as long as possible until terminating exercise due to symptom limitation. Patients were asked to cycle between 60-70 rpm during each exercise trial. Resting data were collected for 3 minutes while the patient sat quietly on the cycle ergometer. Ventilatory parameters, esophageal pressure, oxyhemoglobin saturation and heart rate were measured continuously at rest and throughout each exercise trial. Echocardiography was performed at rest and following obtainment of a steady state at each workload and every 3 minutes at 75% W_{max} as patients exercised to symptom limitation. Immediately following each set of echocardiographic measurements, inspiratory capacity maneuvers were performed to estimate changes in EELV, blood pressure was measured and leg discomfort was recorded using the modified Borg scale. In addition, the sensory and affective dimensions of dyspnea were measured using the multidimensional dyspnea profile (MDP) at rest, immediately upon completion of echocardiographic measurements at 25% and 50% W_{max} , and immediately after obtaining the first set of echocardiographic images at 75% W_{max} . Pilot work previously determined that we could make all of the necessary measurements in a 30-40 second time period. On termination of the exercise test, patients were asked to identify which symptom was responsible for exercise cessation (i.e. dyspnea or leg discomfort). Patients were also asked to describe the sensation of dyspnea in their own words.

2.2.4.4 Volume and Intrathoracic Pressure Measurements

Expired gases were collected and continuously analyzed at rest and during exercise using a calibrated metabolic measurement system (Sensormedics Vmax 29C, SensorMedics, Yorba Linda, CA). The flow signal from the pneumotachograph was integrated to obtain volume. Intrathoracic pressure was measured via a balloon-tipped catheter, using standard procedures as previously performed by our group [75]. More specifically, after applying a topical anaesthetic to the patient's nares and nasal conchae (Xilocaine®, Lidocaine Hydrochloride), a conventional balloon-tipped catheter (Ackrad Laboratories Inc., Cranford, NJ) was advanced into the stomach by sipping a small amount of water through a straw. Participants were asked to perform a brief Valsalva maneuver while the catheter was open to the atmosphere to empty the balloon. The balloon was then inflated to 1.0 ml as per the manufacturer's recommendation. The balloon was then withdrawn gradually until a negative deflection was present during inspiration before being withdrawn another 5-10cm (~40cm from the nose to the tip of the balloon) and fixed at a depth where cardiogenic effects were minimized. The balloon was secured in place by taping it to the patient's nose and cheek. For measurement of esophageal pressure, the balloon catheter was connected to a differential pressure transducer (MP45, Validyne, Northridge, CA) which was calibrated before each test using a water-filled manometer. Signals from the differential pressure transducer were converted to a digital signal using a data acquisition system (Powerlab, ADI Instruments, Colorado Springs, CO). All data were sampled at 100 Hz and stored on a computer for analysis at a later date.

2.2.4.5 Inspiratory Capacity Maneuvers

During the CPET, repetitive inspiratory capacity (IC) maneuvers were performed at rest and every two minutes during exercise. IC maneuvers were also performed following each set of echocardiographic measurements during the discontinuous constant load exercise trials to estimate changes in EELV. This technique assumes that total lung capacity (TLC) does not change with exercise [76, 77]; therefore, $EELV = TLC - IC$ which has previously been shown to be a reliable

technique for measuring EELV during exercise in patients with chronic respiratory disease [76, 77]. At the end of a normal expiration the patient was asked to breathe in without warning and to give an additional effort on top of a maximal inspiration [76].

2.2.4.6 Measurement of Dyspnea

Dyspnea was defined as the sensation of breathlessness or breathing discomfort. The intensity of dyspnea was evaluated using the modified Borg scale. The modified Borg scale was explained to patients by anchoring the end points of the scale to descriptors such that “0” represented “no dyspnea at all”, while “10” indicated “the maximal intensity of dyspnea that the patient had ever previously experienced or could imagine”. Patients were asked to rate the intensity and unpleasantness of dyspnea using the multidimensional dyspnea profile (MDP). Patients were asked to rate “the intensity or strength of the sensation” defined as “how much breathing sensation you feel”, while the unpleasantness of the sensation was defined as “how bad it feels”. The distinction between these two aspects of breathing sensation was made clearer by describing an analogy between shortness of breath and listening to a sound, such as the radio. Volume of the radio was said to be analogous to the intensity of the sensation, while how good or bad the sound on the radio is to hear was said to be analogous to unpleasantness. For example, “music that you dislike can be unpleasant even when the volume is low, and will become more unpleasant as the volume increases” or “music that you like will not be unpleasant, even when the volume increases”. Patients were also asked to describe the sensation of dyspnea in their own words immediately following exercise cessation.

2.2.4.7 Exercise Echocardiography

Echocardiography was performed by a qualified sonographer using a commercial cardiovascular ultrasound system equipped with a 2.5 MHz transducer (IE33, Phillips, Netherlands). Images were obtained in the upright position on the cycle ergometer, after adjusting the seat height to

minimize any lateral movement and the height and angle of the handlebars to allow forward flexion of the torso in an attempt to bring the heart forward in the thoracic cavity. Measurements were made at rest and during exercise at 25%, 50% and 75% $W_{\max}$. Exercise measurements were made after the subject had achieved a steady state as determined by the change in $\dot{V}O_2 < 0.1 \text{ L}\cdot\text{min}^{-1}$ and heart rate within $5 \text{ beats}\cdot\text{min}^{-1}$. A discontinuous protocol, where patients were given ~10 minutes rest between exercise at each intensity, was utilized so that subjects could maximize their ability to maintain steady state for longer while holding a stable body position, which allowed more optimal image acquisition. Left ventricular diastolic filling and relaxation and systolic function were quantified at rest by measuring: 1) peak early (E) and late (A) diastolic filling velocities across the mitral valve measured by pulsed wave Doppler from the apical four-chamber view at the tips of the mitral valve leaflets; 2) peak early (E) and late (A) diastolic velocity and peak systolic velocity measured by pulsed wave tissue Doppler imaging from the apical four-chamber view at the septal and lateral aspects of the mitral annulus; 3) right ventricular systolic pressure was estimated by continuous wave Doppler echocardiography using the modified Bernoulli equation ($p = 4v^2 + \text{right atrial pressure [RAP]}$), where v = the peak tricuspid regurgitant velocity and RAP was predicted using the “sniff test”). More specifically, if with a forceful sniff the inferior vena cava (IVC) collapsed $< 50\%$ the RAP was assumed to be 3 mmHg. If the IVC collapsed ~50% RAP was considered 8 mmHg and if the RAP collapsed $< 50\%$ it was considered 15 mmHg. The apical four-chamber and short axis views were obtained to ascertain and record optimal tricuspid flow signals. Left ventricular diastolic filling and systolic function were quantified at rest and during exercise at 25%, 50% and 75% $W_{\max}$ by measuring: ejection fraction, end-diastolic and end-systolic volumes and stroke volume derived by the modified Simpson’s method [78], where the total left ventricular volume is calculated from the summation of a stack of elliptical discs utilizing the apical four and two-chamber views during rest and exercise. The ECG trace was used to accurately time the beginning and end of systolic ejection. End-diastole was taken as the frame before mitral valve closure, and end-systole as the frame prior to mitral valve opening. Endocardial border tracing of end-diastolic and end-systolic images were then performed according to American Society of Echocardiography recommendations [78]. A minimum of three measurements for each image were analyzed and averaged for the calculation of each cardiac variable. All

echocardiograms were analyzed offline using EchoPac Software (GE Healthcare, Milwaukee, WI, United States). The coefficient of variation in the two echo technicians in this study for measurements of stroke volume range from 5.7 - 21.9% for measurements made at rest and during exercise at 25%, 50% and 75% W_{max} .

2.2.4.8 Statistical Analysis

Descriptive statistics utilized mean $\pm$ SD. Before applying statistical methods that assumed normalcy, a Shapiro-Wilks test was performed. To ascertain any association between the change in neuromechanical coupling and dyspnea, simple regression analysis using Pearson correlations was performed. The primary outcome was the association between neuromechanical uncoupling ($P_{insp}/P_{Imax} : V_T/VC$) measured at maximal exercise in the incremental exercise test and at an isotime during the constant load trials and ratings of exertional dyspnea. Pearson correlations were also used to investigate any association between other secondary outcome variables (i.e. ventilatory parameters, respiratory pressures, echocardiographic measurements, etc.) and exertional dyspnea. Finally, Pearson correlations were used to investigate any association between exertional dyspnea, ventilatory parameters, and echocardiographic measurements and exercise tolerance during the 75% W_{max} trial. All analysis was performed using commercially available software (Statistica, Statsoft, Oklahoma City, OK). Differences between groups were compared with two-tailed independent t-tests.

To compare responses between differing intensities of exercise in the constant-load trials, a one-way repeated measures ANOVA was performed. The same test was used to look at responses over time in the exercise tolerance trial. Where there was a significant main effect for exercise intensity or time, pairwise post hoc analysis using the Tukey test was run. For non-normally distributed data we performed a Friedman repeated measures ANOVA on ranks. Where there was a main effect for exercise intensity or time a Wilcoxon rank-sum test was run. The alpha level was set *a priori* at 0.05 for all analysis.

2.3 Results

2.3.1 Participant Characteristics

A total of 75 patients were recruited from the Kelowna thoracic surgery clinic, of whom 29 met all eligibility criteria. Reasons for non-eligibility are listed in Figure 2.1. Of these patients, 15 patients declined consent for participation. Reasons cited for non-consent included being uninterested (n=3), unable to commit (n=3), feeling unwell (n=2), declining the esophageal balloon catheter (n=2), or we were unable to contact the patient following receipt of the consent to contact letter (n=5). One patient was excluded after completing the PFT due to uncontrolled hypertension. As a result, 13 patients completed the study protocol. Esophageal pressures were measured in seven patients. Of the remaining six patients, three patients declined insertion of the esophageal balloon catheter on arrival, two patients experienced uncontrollable cough during introduction of the esophageal balloon, and the esophageal balloon was retracted from one patient due to irritation and pain resulting from scar tissue associated with a previous tracheotomy.

Participant characteristics are depicted in Table 2.1. Participants were predominantly female (77%). The age of participants ranged from 45 to 80 years with a mean age of 68 ± 9 years. All participants previously underwent pulmonary resection for stage I-IIIa NSCLC. Mean time from surgery was 2.5 ± 1.9 years and ranged from 5.5 months to 5.7 years.

Compared to controls, patients with NSCLC had a significantly lower FEV₁, FVC, FEV₁/FVC, TLC and D_{LCO} (Table 2.1). There were no significant differences in FRC or RV between groups. However, patients with NSCLC had a significantly higher RV when expressed relative to TLC compared to controls. The MIP was normal among patients with NSCLC, while MEP was substantially reduced compared to predicted values.

Figure 2.1 Study flow.

Abbreviations: PFT, pulmonary function test; CPET, cardiopulmonary exercise test; CLT, constant load trial; W_{max} , maximum power output achieved in the incremental exercise test.

Table 2.1 Participant Characteristics

	NSCLC (n = 13)	Control (n = 9)
Male:Female	3:10 (23)	3:6 (33)
Age, yr	68 ± 9	64 ± 6
Weight, kg	77 ± 16	66 ± 8
BMI, kg/m ²	28 ± 6	25 ± 2
Smoking History		
Current	3 (23)	0 (0)
Former	9 (69)	2 (22)
Never	1 (8)	7 (78)
Histologic Features		
Adenocarcinoma	9 (69)	
Squamous Cell Carcinoma	4 (31)	
Undifferentiated	0 (0)	
Stage		
IA	7 (54)	
IB	3 (23)	
IIB	2 (15)	
IIIA	1 (8)	
Extent of Resection		
Wedge	3 (23)	
Lobectomy	8 (62)	
Pneumonectomy	2 (15)	
Surgical Procedure		
VATS	7 (54)	
Open Thoracotomy	6 (46)	
Time Since Surgery (Years)	2.5 ± 1.9	
Adjuvant Therapy		
Chemotherapy	5 (38)	
Radiotherapy	1 (8)	
Concomitant Comorbidities		
COPD	5 (38)	0 (0)
Hypercholesterolemia	2 (15)	1 (11)
Hypertension	4 (31)	3 (33)
Mental Illness	2 (15)	1 (11)
Osteoarthritis	4 (31)	0 (0)
Osteoporosis	1 (8)	1 (11)
Rheumatoid Arthritis	1 (8)	0 (0)
Pulmonary Function		
FEV ₁ , L	1.57 ± 0.69 (64 ± 25)*	3.06 ± 0.64 (120 ± 16)
FVC, L	3.01 ± 0.77 (97 ± 18)*	4.00 ± 0.93 (124 ± 15)
FEV ₁ /FVC, %	51 ± 15*	77 ± 5
TLC, L	5.34 ± 1.05 (98 ± 16)*	6.18 ± 1.15 (111 ± 10)
FRC, L	3.44 ± 0.99 (113 ± 32)	3.17 ± 0.60 (103 ± 14)
RV, L	2.21 ± 0.70 (101 ± 32)	1.94 ± 0.41 (90 ± 19)
RV/TLC, %	42 ± 11*	32 ± 6
D _{LCO} , ml/mmHg/min	13.7 ± 5.0 (62 ± 22)*	19.5 ± 4.2 (85 ± 10)
D _{LCO} /V _A , ml/mmHg/min/L	3.50 ± 1.06 (83 ± 25)	3.73 ± 0.33 (87 ± 7)
MIP, cm H ₂ O	75 ± 26 (98 ± 37)	
MEP, cm H ₂ O	95 ± 40 (64 ± 26)	

Values are no. (%) or means ± SD (% predicted). *Abbreviations:* BMI, body mass index; VATS, video-assisted thoracoscopic surgery; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; D_{LCO}, diffusion capacity for carbon monoxide; D_{LCO}/V_A, D_{LCO} corrected for alveolar volume; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure. Significantly different from control: *p<0.05.

2.3.2 Responses to Incremental Exercise in Patients with NSCLC

The cardiopulmonary responses to incremental exercise in patients with NSCLC are depicted in Figure 2.2. Patients with NSCLC demonstrated a normal HR response to incremental exercise, achieving a maximum heart rate (HR) of 129 ± 13 bpm equivalent to $81 \pm 7\%$ of predicted maximum (Table 2.2). Mean arterial pressure (MAP), oxyhemoglobin saturation (S_pO_2), ventilation (V_E), tidal volume (V_T) and breathing frequency also exhibited normal responses to incremental exercise. Patients with NSCLC achieved a peak V_E of 50 ± 15 L·min⁻¹. Mean peak V_E expressed relative to predicted maximum voluntary ventilation (MVV) was $98 \pm 20\%$. Eight patients achieved $V_{Epeak}\%MVV > 85\%$ and were therefore considered to be ventilatory limited [74]. An additional two patients also achieved $HR_{max} > 90\%$ and were therefore both ventilatory and cardiovascular limited [74]. The remaining three patients did not meet criteria for either ventilatory or cardiovascular limitation.

As depicted in Figure 2.3, changes in operational lung volumes throughout exercise were relatively normal in patients with NSCLC. EILV increased towards TLC throughout exercise and reached $92 \pm 4\%$ of TLC at end exercise. Subsequently, IRV was reduced 65% from rest to end exercise, reaching an IRV of 0.43 ± 0.22 L at peak exercise. The esophageal pressure swing ($P_{exp} - P_{insp}$) increased from 4.4 ± 1.6 cm H₂O at rest to 25.3 ± 12.6 at end exercise (Figure 2.3). Peak P_{insp} and P_{exp} reached $19 \pm 7\%$ and $10 \pm 9\%$ of MIP and MEP, respectively. NMU was unchanged throughout exercise while mNMU increased significantly from rest to peak exercise ($p = 0.011$), demonstrating that while negative pressures are not significantly increased there is a greater pressure swing being generated to meet ventilatory demands.

Mean peak ratings of dyspnea and leg discomfort on exercise termination were 5 ± 2 and 6 ± 2 , respectively. The most common reasons for ending exercise cited by patients were leg discomfort (46%), dyspnea (31%) or a combination of the two symptoms (23%).

Figure 2.2 Cardiopulmonary responses to incremental exercise in patients with NSCLC and controls.

Abbreviations: V_E , ventilation; V_T , tidal volume; SpO_2 , oxyhemoglobin saturation; HR, heart rate; MAP, mean arterial pressure. Significantly different from control: * $p < 0.05$.

Figure 2.3 Symptom, operational lung volume and pressure responses to incremental exercise in patients with NSCLC and controls.

Abbreviations: V_E , ventilation; TLC, total lung capacity; EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume; IRV, inspiratory reserve volume; P_{es} , esophageal pressure; P_{exp} , expiratory esophageal pressure; P_{insp} , inspiratory esophageal pressure; NMU, neuromechanical uncoupling calculated as $P_{insp}/MIP : V_T/VC$; mNMU, modified NMU calculated as $P_{exp-insp}/(MEP-MIP) : V_T/VC$. Significantly different from control: * $p < 0.05$.

Table 2.2 Peak Incremental Exercise Test Results

	NSCLC (n = 13)	Control (n = 9)
Power Output, watts	76 ± 28*	104 ± 32
% predicted	71 ± 20*	92 ± 8
VO _{2peak} , L·min ⁻¹	1.32 ± 0.42	1.58 ± 0.46
VO _{2peak} , ml·kg ⁻¹ ·min ⁻¹	17.1 ± 4.5*	22.7 ± 3.8
% predicted	81 ± 20*	97 ± 9
HR, beats·min ⁻¹	129 ± 13*	151 ± 11
% predicted	81 ± 7*	98 ± 7
SBP, mmHg	178 ± 19	192 ± 17
DBP, mmHg	92 ± 12	86 ± 8
MAP, mmHg	120 ± 11	121 ± 9
S _p O ₂ , %	94 ± 3*	97 ± 2
ΔS _p O ₂ , %	-3 ± 3	-1 ± 2
V _E , L·min ⁻¹	50 ± 15*	65 ± 16
% predicted	85 ± 17*	56 ± 11
V _T , L	1.42 ± 0.47*	2.13 ± 0.54
f, breaths·min ⁻¹	34 ± 4*	28 ± 5
IC, L	1.86 ± 0.64*	3.01 ± 0.78
ΔIC, L	-0.11 ± 0.50*	0.07 ± 0.22
IRV, L	0.43 ± 0.22*	0.88 ± 0.48
O ₂ Pulse, ml/beat	9.9 ± 2.6	10.9 ± 3.3
P _{ET} CO ₂ , mmHg	34.6 ± 3.9	34.2 ± 3.3
P _{ET} O ₂ , mmHg	108.8 ± 5.1	111.9 ± 5.1
RER	1.07 ± 0.08*	1.17 ± 0.11
P _{insp} , cm H ₂ O	-15.0 ± 5.4	
P _{insp} , %MIP	19 ± 7	
P _{exp} , cm H ₂ O	10.3 ± 8.8	
P _{exp} , %MEP	10 ± 9	
NMU	0.48 ± 0.33	
mNMU	0.33 ± 0.19	
Dyspnea (/10)	5 ± 2	5 ± 2
Leg Discomfort (/10)	6 ± 2	6 ± 2
Reason For Ending Exercise		
Dyspnea	4 (31)	1 (11)
Leg Discomfort	6 (46)	7 (78)
Both	3 (23)	1 (11)
Exercise Limitation		
Ventilatory	8 (62)	0 (0)
Cardiovascular	0 (0)	8 (89)
Both	2 (15)	0 (0)
None	3 (23)	1 (11)

Values are means ± SD or no. (%). *Abbreviations:* VO_{2peak}, peak oxygen consumption; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; S_pO₂, oxyhemoglobin saturation; ΔS_pO₂, change in S_pO₂ from resting values; V_E, ventilation; V_T, tidal volume; f, breathing frequency; IC, inspiratory capacity; ΔIC, change in IC from resting values; IRV, inspiratory reserve volume; P_{ET}CO₂, end-tidal carbon dioxide tension; P_{ET}O₂, end-tidal oxygen tension; RER, respiratory exchange ratio; P_{insp}, inspiratory esophageal pressure; MIP, maximal inspiratory pressure; P_{exp}, expiratory esophageal pressure; MEP, maximal expiratory pressure; NMU, neuromechanical uncoupling calculated as P_{insp}/MIP : V_T/VC; mNMU, modified NMU calculated as P_{exp-insp}/(MEP-MIP) : V_T/VC. Significantly different from control: *p<0.05.

2.3.3 Responses to Incremental Exercise in Patients with NSCLC Compared to Controls

In comparison to healthy controls, patients with NSCLC achieved a significantly lower peak power output, RER and relative $\text{VO}_{2\text{peak}}$ (Table 2.2). HR_{max} was also significantly reduced in the NSCLC group in comparison to controls. There were no differences in the blood pressure response to incremental exercise between the two groups; however, patients with NSCLC exhibited significantly greater desaturation at peak exercise, with a reduction in S_pO_2 to $94 \pm 3\%$. The V_T response was similar between the two groups, while peak V_T was significantly lower in patients with NSCLC. Breathing frequency appeared to be increased for a given workload throughout exercise in patients with NSCLC relative to controls and was significantly greater than that of controls at peak exercise. This resulted in a leftward shift of the V_E response in patients with NSCLC in comparison to the control group, whereby patients with NSCLC achieved a peak V_E at a lower power output. Peak V_E expressed relative to predicted MVV was significantly higher in NSCLC patients than controls ($98 \pm 20\%$ vs. $60 \pm 5\%$, respectively).

There were no significant differences in dyspnea intensity for a given workload or ventilation at submaximal levels between groups. Furthermore, there was no significant difference in peak dyspnea intensity despite a significant reduction in peak power output in the NSCLC group. Furthermore, absolute EILVs and EELVs were not different between groups. However, when expressed relative to TLC, patients with NSCLC exhibited significantly increased EILVs throughout exercise compared to controls. EELV expressed relative to TLC was also elevated in patients with NSCLC. As a result of breathing at these higher relative lung volumes, IRV was significantly reduced in patients with NSCLC throughout exercise (Figure 2.3).

2.3.4 Responses to Discontinuous Constant-Load Exercise in Patients with NSCLC

Resting echocardiographic measurements are presented in Table 2.3. Peak E velocity was 58.3 ± 14.3 cm/s and peak A velocity was 68.9 ± 13.5 cm/s, being statistically lower than controls. However, there were no significant differences in the E/A ratio between patients with NSCLC (0.8 ± 0.1) and controls (0.9 ± 0.2). E' medial was 6.43 ± 0.85 cm/s and A' medial was 11.30 ± 3.24 cm/s in patients with NSCLC. Patients with NSCLC demonstrated normal cardiopulmonary responses to differing intensities of constant load exercise, as depicted in Figure 2.4. MAP increased significantly from 95 ± 10 mmHg at rest to 117 ± 10 mmHg at 75% W_{max} . V_E , V_T and breathing frequency increased significantly with increasing exercise intensity but S_pO_2 was not significantly reduced at 75% W_{max} compared to rest. P_{exp} increased significantly from rest to 50% W_{max} and 75% W_{max} , while there was no change in P_{insp} . NMU and mNMU were essentially unchanged between the exercise trials. Operational lung volume responses were also largely normal in patients with NSCLC (Figure 2.5). There was a significant effect of exercise intensity for absolute EILV, EILV%TLC, IRV and IRV%TLC. There was no change in EELV or EELV%TLC.

Symptom responses to differing intensities of exercise in patients with NSCLC are illustrated in Figure 2.6. There was a significant effect of exercise intensity for all symptoms including sensory intensity, unpleasantness, leg discomfort, and the ratio of unpleasantness (A1) to sensory intensity (SI). Mean ratings of the five sensory qualities of dyspnea are presented in Figure 2.7. Ratings for each of the five sensory qualities of dyspnea at 75% W_{max} were significantly greater than at all other time points. The primary sensations of exertional dyspnea reported by patients with NSCLC were the sensations of work / effort, unsatisfied inspiration or air hunger, and breathing rapidly and heavily. Patients with NSCLC did not report considerable mental effort to breathe or chest tightness.

In patients with NSCLC, there was a significant increase in EDV from rest to 25% W_{max} and from rest to 75% W_{max} ; however, there was no significant effect of intensity for EDV when indexed to body surface area (BSA) (end-diastolic volume index [EDVI]) (Figure 2.8). There was no effect of

exercise intensity for ESV or ESVI. SV increased 30% from rest to 25% W_{max} but exhibited no further increases with augmented exercise intensities. A similar response was observed for EF, in which EF increased 8% from rest to 25% W_{max} . HR and Q exhibited normal responses to differing intensities of exercise, also exhibiting significant increases from rest to 75% W_{max} .

Table 2.3 Discontinuous Constant-Load Trial Responses

	NSCLC Rest	Control Rest	NSCLC 25% W _{max}	Control 25% W _{max}	NSCLC 50% W _{max}	Control 50% W _{max}	NSCLC 75% W _{max}	Control 75% W _{max}
Power Output, watts			19 ± 8*Φ	27 ± 3	39 ± 14*†‡Φ	51 ± 3	63 ± 22*†‡	76 ± 3
HR, beats·min ⁻¹	82 ± 12	78 ± 9	99 ± 12*	96 ± 5	110 ± 13*†	109 ± 6	127 ± 13*†‡	131 ± 8
SBP (mmHg)	122 ± 15	129 ± 14	144 ± 21*	140 ± 14	157 ± 21*†	158 ± 17	175 ± 18*†‡	180 ± 14
DBP (mmHg)	82 ± 10	80 ± 10	83 ± 10	80 ± 11	82 ± 9	80 ± 10	89 ± 11	83 ± 11
MAP (mmHg)	95 ± 11	96 ± 11	104 ± 12*	100 ± 11	107 ± 10	106 ± 11	117 ± 10*†‡	115 ± 11
S _p O ₂ , %	97 ± 1	97 ± 0	96 ± 2*	96 ± 1	95 ± 2*	97 ± 1	95 ± 4	97 ± 2
V _E , L·min ⁻¹	12 ± 4	10 ± 3	22 ± 8*	18 ± 6	29 ± 7*†	30 ± 9	39 ± 12*†‡	50 ± 20
V _T , L	0.70 ± 0.18		1.05 ± 0.27*		1.28 ± 0.38*†		1.53 ± 0.48*†‡	
f, breaths·min ⁻¹	18 ± 4		21 ± 4*		23 ± 4*†		26 ± 4*†‡	
IC (L)	1.91 ± 0.51		1.96 ± 0.64		1.98 ± 0.59		1.98 ± 0.61	
P _{insp} , cm H ₂ O	-9.6 ± 5.7		-12.7 ± 6.9		-13.5 ± 4.2		-13.6 ± 6.2	
P _{insp} , %MIP	11 ± 5		15 ± 6		17 ± 3		18 ± 7	
P _{exp} , cm H ₂ O	-3.3 ± 3.0		1.5 ± 5.8		2.1 ± 5.7*		4.8 ± 4.1*	
P _{exp} , %MEP	3 ± 2		2 ± 6		2 ± 6		4 ± 3	
NMU	0.51 ± 0.18		0.45 ± 0.17		0.44 ± 0.13		0.44 ± 0.24	
mNMU	0.15 ± 0.04		0.22 ± 0.08		0.21 ± 0.08		0.24 ± 0.12	
Dyspnea								
Intensity (/10)	0 ± 1		1 ± 1*		2 ± 1*†		3 ± 1*†‡	
Unpleasantness (/10)	0 ± 1		1 ± 1		2 ± 2*		3 ± 1*†‡	
Leg Discomfort (/10)	0 ± 1		1 ± 2		3 ± 2*†		4 ± 1*†‡	
EDV, ml	52 ± 16	64 ± 22	63 ± 16*	71 ± 25	61 ± 18	74 ± 23	64 ± 21*	73 ± 26
EDVI, ml/m ²	28.4 ± 7.1	37.8 ± 17.1	34.3 ± 6.3	42.0 ± 19.2	30.3 ± 12.4	43.7 ± 18.2	31.0 ± 13.6	43.0 ± 19.9
ESV, ml	20 ± 7	23 ± 11	20 ± 6	21 ± 9	18 ± 6	18 ± 7	18 ± 7	17 ± 8
ESVI, ml/m ²	10.6 ± 3.0	13.6 ± 7.7	10.6 ± 2.6	12.6 ± 6.9	9.7 ± 2.4	10.6 ± 4.4	9.5 ± 2.9	9.9 ± 5.2
SV, ml	33 ± 11	39 ± 9	43 ± 12*	50 ± 15	44 ± 15*	55 ± 20	46 ± 19*	56 ± 21
SI, ml/m ²	17.8 ± 4.9	23.1 ± 7.3	23.7 ± 5.8*	29.2 ± 12.0	23.7 ± 7.0*	32.8 ± 15.8	24.5 ± 9.2*	33.1 ± 16.5
Q, L·min ⁻¹	2.7 ± 1.1	3.0 ± 0.7	4.3 ± 1.4*	4.6 ± 1.3	4.8 ± 1.9*	5.9 ± 2.2	5.9 ± 2.8*†‡	7.1 ± 2.6
CI, L·min ⁻¹ /m ²	1.5 ± 0.5	1.7 ± 0.5	2.3 ± 0.7*	2.7 ± 1.0	2.6 ± 0.9*	3.5 ± 1.6	3.2 ± 1.4*†‡	4.2 ± 2.0
EF, %	63 ± 6	65 ± 8	68 ± 8*	71 ± 5	70 ± 7*	75 ± 8	71 ± 9*	77 ± 8

Values are means ± SD or no. (%). NSCLC rest n=13; 25% W_{max} n=13; 50% W_{max} n=12; 75% W_{max} n=10. Control n=9 at all intensities. *Abbreviations*: HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; S_pO₂, oxyhemoglobin saturation; V_E, ventilation; V_T, tidal volume; f, breathing frequency; IC, inspiratory capacity; P_{insp}, inspiratory esophageal pressure; MIP, maximal inspiratory pressure; P_{exp}, expiratory esophageal pressure; MEP, maximal expiratory pressure; NMU, neuromechanical uncoupling calculated as P_{insp}/MIP : V_T/VC; mNMU, modified neuromechanical uncoupling calculated as P_{exp-insp}/(MEP-MIP) : V_T/VC; EDV, end-diastolic volume; EDVI, end-diastolic volume index; ESV, end-systolic volume; ESVI, end-systolic volume index; SV, stroke volume; SI, stroke index; Q, cardiac output; CI, cardiac index; EF, ejection fraction. Significantly different from control: Φ p<0.05. *versus rest, p<0.05. †versus 25% W_{max}, p<0.05. ‡versus 50% W_{max}, p<0.05. The assumptions of ANOVA were not met so non-parametric statistics were run for: MAP, S_pO₂.

Figure 2.4 Cardiopulmonary responses to differing intensities of exercise in patients with NSCLC and controls.

Abbreviations: MAP, mean arterial pressure; S_pO_2 , oxyhemoglobin saturation; V_E , ventilation; V_T , tidal volume; P_{es} , esophageal pressure; P_{insp} , inspiratory esophageal pressure; P_{exp} , expiratory esophageal pressure; NMU, neuromechanical uncoupling calculated as $P_{insp}/MIP : V_T/VC$; mNMU, modified NMU calculated as $P_{exp-insp}/(MEP-MIP) : V_T/VC$. No significant differences NSCLC vs. control. *versus rest, $p < 0.05$. †versus 25% W_{max} , $p < 0.05$. ‡versus 50% W_{max} , $p < 0.05$. The assumptions of ANOVA were not met so non-parametric statistics were run for: MAP, S_pO_2 .

Figure 2.5 Operational lung volume responses to differing intensities of exercise in patients with NSCLC.

Abbreviations: TLC, total lung capacity; EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume; IRV, inspiratory reserve volume. *versus rest, $p < 0.05$. †versus 25% W_{max} , $p < 0.05$. ‡versus 50% W_{max} , $p < 0.05$.

Figure 2.6 Symptom responses to differing intensities of exercise in patients with NSCLC.

Abbreviations: A1, dyspnea unpleasantness; SI, dyspnea intensity. * versus rest, $p < 0.05$. † versus 25% W_{max} , $p < 0.05$. ‡ versus 50% W_{max} , $p < 0.05$.

Figure 2.7 Sensory qualities of dyspnea in response to differing intensities of exercise in patients with NSCLC.

Abbreviations: W-E, work/effort; A-H, unsatisfied inspiration/air hunger; M-E, mental effort; tight, chest tightness; heavy, breathing rapidly/heavily. *versus rest, $p < 0.05$. †versus 25% W_{max} , $p < 0.05$. ‡versus 50% W_{max} , $p < 0.05$. The assumptions of ANOVA were not met so non-parametric statistics were run for: A-H, M-E, Tight.

Figure 2.8 Cardiac responses to differing intensities of exercise in patients with NSCLC and controls.

Abbreviations: EDV, end-diastolic volume; EDVI, end-diastolic volume index; ESV, end-systolic volume; ESVI, end-systolic volume index; SV, stroke volume; SI, stroke index; HR, heart rate; Q, cardiac output; CI, cardiac index; EF, ejection fraction. No significant differences NSCLC vs. control. *versus rest, p<0.05. †versus 25% W_{max} , p<0.05. ‡versus 50% W_{max} , p<0.05.

2.3.5 Responses to Discontinuous Constant-Load Exercise in Patients with NSCLC Compared to Controls

When comparing patients with NSCLC to controls, the mean power outputs at 25% and 50% $W_{\max}$, but not at 75% $W_{\max}$, were significantly reduced among patients with NSCLC. Despite this, there were no significant differences in the cardiopulmonary responses to differing intensities of exercise between patients with NSCLC and controls. EDV was reduced on average by 12% at 75% $W_{\max}$ compared to controls, but this did not reach significance ($p = 0.415$). When indexed to BSA, EDVI was reduced on average by 21% at 75% $W_{\max}$ compared to controls, but this was also not significant ($p = 0.219$). There were no differences between the groups for HR, SV or Q.

There were no significant differences in the change from rest to 75% $W_{\max}$ in SBP, DBP, MAP, S_pO_2 or V_E between patients with NSCLC and controls. However, patients with NSCLC increased HR significantly less than controls from rest to 75% $W_{\max}$ ($p=0.014$), with mean increases in HR of $45 \pm \text{bpm}$ and $54 \pm \text{bpm}$, respectively. When comparing the change from rest to 75% $W_{\max}$ between the two groups, there were also no significant differences found for any of the cardiac parameters either before or after indexing for BSA.

2.3.6 Responses to Constant-Load Exercise to Symptom Limitation in Patients with NSCLC

The cardiopulmonary responses to constant-load exercise to symptom limitation at 75% $W_{\max}$ in patients with NSCLC are depicted in Figure 2.9. Patients with NSCLC achieved a peak V_E of $41 \pm 12 \text{ L}\cdot\text{min}^{-1}$ or $62 \pm 16\%$ of predicted maximum. Peak V_E expressed relative to predicted MVV was $71 \pm 19\%$. P_{exp} increased significantly from rest to 50% $W_{\max}$ and 75% $W_{\max}$, while there were no significant changes in P_{insp} . NMU and mNMU were unchanged throughout the trial.

Similar to the response observed during incremental exercise, EILV increased significantly from rest and reached $92 \pm 6\%$ of TLC at end exercise, while IRV declined 66% from rest to end exercise to an IRV of 0.43 ± 0.27 L. EELV was unchanged throughout the trial.

There was a significant effect of exercise intensity for dyspnea intensity. Furthermore, there was a significant increase from rest in ratings of dyspnea unpleasantness, leg discomfort, and the relationship between dyspnea unpleasantness and intensity. Mean ratings of dyspnea intensity and leg discomfort on exercise termination were 5 ± 1 and 5 ± 2 , respectively. The most common reasons for ending exercise cited by patients were leg discomfort (40%), dyspnea (30%) or a combination of the two symptoms (10%). Other reasons for exercise cessation included experiencing throat dryness and being generally uncomfortable (10%).

Cardiac responses are presented in Figure 2.12. EDV was seen to increase significantly from rest to steady-state; however, there was no significant difference in EDV compared to rest at end exercise. In contrast to the pattern observed during incremental exercise, ESV was significantly reduced compared to rest at both steady-state and end exercise. These responses persisted after indexing for BSA. SV appeared to increase from rest to steady-state; however, this increase was not statistically significant until being indexed to BSA. Patients with NSCLC demonstrated a normal HR response, achieving a maximum HR of 131 ± 15 bpm equivalent to $82 \pm 8\%$ of predicted maximum. Q increased approximately two-fold from rest to steady-state before reaching a plateau. EF was also seen to increase 16% from rest to end exercise.

Table 2.4 Constant Load Trial End Exercise Results

	NSCLC
Time, seconds	349 ± 197
VO ₂ , L·min ⁻¹	1.27 ± 0.34
VO ₂ , ml·kg ⁻¹ ·min ⁻¹	16.9 ± 3.3
% predicted	77 ± 19
HR, beats·min ⁻¹	131 ± 15
% predicted	82 ± 8
SBP, mmHg	175 ± 15
DBP, mmHg	89 ± 12
MAP, mmHg	118 ± 11
S _p O ₂ , %	95 ± 4
ΔS _p O ₂ , %	-3 ± 4
V _E , L·min ⁻¹	41 ± 12
% predicted	62 ± 16
V _T , L	1.51 ± 0.49
f, breaths·min ⁻¹	28 ± 4
IC, L	1.97 ± 0.62
ΔIC, L	-0.10 ± 0.48
IRV, L	0.46 ± 0.30
O ₂ Pulse, ml/beat	9.7 ± 2.3
P _{insp} , cm H ₂ O	-13.3 ± 5.7
P _{insp} , %MIP	17 ± 6
P _{exp} , cm H ₂ O	5.9 ± 4.3
P _{exp} , %MEP	5 ± 3
NMU	0.45 ± 0.25
mNMU	0.26 ± 0.14
Dyspnea	
Intensity (/10)	5 ± 1
Unpleasantness (/10)	4 ± 1
Leg Discomfort (/10)	5 ± 2
Reason For Ending Exercise	
Dyspnea	4 (40)
Leg Discomfort	4 (40)
Both	1 (10)
Other	1 (10)
Dyspnea Description	
Work/Effort	1 (10)
Unsatisfied Inspiration/Air Hunger	3 (30)
Unsatisfied Inspiration & Expiration	1 (10)
Breathing Rapidly/Heavily	4 (40)
Exercise Limitation	
Ventilatory	3 (30)
Cardiovascular	2 (20)
Both	0 (0)
None	5 (50)
EDV, ml	63 ± 21
EDVI, ml/m ²	33.4 ± 9.3
ESV, ml	17 ± 6
ESVI, ml/m ²	8.8 ± 2.9
SV, ml	46 ± 19
SI, ml/m ²	24.7 ± 9.1
Q, L·min ⁻¹	6.0 ± 2.8
CI, L·min ⁻¹ /m ²	3.0 ± 1.6
EF, %	72 ± 10

Values are means ± SD or no. (%). Constant load trial was performed at 75% W_{max} (n=10). *Abbreviations:* VO₂, oxygen consumption; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; S_pO₂, oxyhemoglobin saturation; ΔS_pO₂, change in S_pO₂ from resting values; V_E, ventilation; V_T, tidal volume; f, breathing frequency; IC, inspiratory capacity; ΔIC, change in IC from resting values; IRV, inspiratory reserve volume; P_{insp}, inspiratory esophageal pressure; MIP, maximal inspiratory pressure; P_{exp}, expiratory esophageal pressure; MEP, maximal expiratory pressure; NMU, neuromechanical uncoupling calculated as P_{insp}/MIP : V_T/VC; mNMU, modified neuromechanical uncoupling calculated as P_{exp}·insp/(MEP-MIP) : V_T/VC; EDV, end-diastolic volume; EDVI, end-diastolic volume index; ESV, end-systolic volume; ESVI, end-systolic volume index; SV, stroke volume; SI, stroke index; Q, cardiac output; CI, cardiac index; EF, ejection fraction.

Figure 2.9 Cardiopulmonary responses to constant-load exercise to symptom limitation in patients with NSCLC.

Measurements were made at rest, steady-state following echocardiography, and end exercise. *Abbreviations:* MAP, mean arterial pressure; SpO₂, oxyhemoglobin saturation; V_E , ventilation; V_T , tidal volume; P_{es} , esophageal pressure; P_{insp} , inspiratory esophageal pressure; P_{exp} , expiratory esophageal pressure; NMU, neuromechanical uncoupling calculated as $P_{insp}/MIP : V_T/VC$; mNMU, modified neuromechanical uncoupling calculated as $P_{exp-insp}/(MEP-MIP) : V_T/VC$. *versus rest, $p < 0.05$. †versus 25% W_{max} , $p < 0.05$. ‡versus 50% W_{max} , $p < 0.05$.

Figure 2.10 Operational lung volume responses to constant-load exercise to symptom limitation in patients with NSCLC.

Measurements were made at rest, steady-state following echocardiography, and end exercise. *Abbreviations:* TLC, total lung capacity; EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume; IRV, inspiratory reserve volume. **versus* rest, $p < 0.05$. †*versus* 25% W_{max} , $p < 0.05$. ‡*versus* 50% W_{max} , $p < 0.05$. The assumptions of ANOVA were not met so non-parametric statistics were run for all variables.

Figure 2.11 Symptom responses to constant-load exercise to symptom limitation in patients with NSCLC.

Measurements were made at rest, steady-state following echocardiography, and end exercise. *Abbreviations:* A1, dyspnea unpleasantness; SI, dyspnea intensity. * *versus* rest, $p < 0.05$. † *versus* 25% W_{max} , $p < 0.05$. ‡ *versus* 50% W_{max} , $p < 0.05$.

Figure 2.12 Cardiac responses to constant-load exercise to symptom limitation in patients with NSCLC. Measurements were made at rest, steady-state following echocardiography, and end exercise. *Abbreviations:* EDV, end-diastolic volume; EDVI, end-diastolic volume index; ESV, end-systolic volume; ESVI, end-systolic volume index; SV, stroke volume; SI, stroke index; HR, heart rate; Q, cardiac output; CI, cardiac index; EF, ejection fraction. *versus rest, $p < 0.05$. †versus 25% W_{max} , $p < 0.05$. ‡versus 50% W_{max} , $p < 0.05$. The assumptions of ANOVA were not met so non-parametric statistics were run for: Q, CI, EF.

2.3.7 Correlates of Exertional Dyspnea and Exercise Tolerance in Patients with NSCLC

There were no significant correlations observed between ventilatory or cardiovascular parameters and exertional dyspnea or exercise tolerance in patients with NSCLC, with the exception of a significant correlation between the resting E/A ratio and exercise tolerance ($r^2 = 0.58$; $p = 0.035$). The ratio of unpleasantness to sensory intensity at end exercise was significantly correlated with P_{insp} ($r^2 = 0.83$; $p = 0.004$) and IRV ($r^2 = 0.31$; $p = 0.048$). There was also a significant correlation between the sensory quality work / effort at end exercise and IRV ($r^2 = 0.32$; $p = 0.046$).

2.4 Discussion

Dyspnea is a frequent and debilitating symptom reported by patients with NSCLC after pulmonary resection [34, 37]. Shortness of breath has a profound negative impact on HRQOL and is an independent predictor of mortality in patients with NSCLC [34, 49]. The mechanisms responsible for dyspnea in cancer patients remain understudied. We therefore set out to explore the major factors contributing to exertional dyspnea in patients with NSCLC after pulmonary resection and to determine the role of dyspnea in exercise intolerance. Additionally, we aimed to investigate whether the cardiovascular system contributes to dyspnea and exercise intolerance in patients with NSCLC.

The primary novel findings of this study were that patients with NSCLC reported greater intensity of dyspnea for a given power output when compared to healthy controls, particularly as patients approached maximal exercise capacity. However, there were no significant correlations observed between ventilatory or cardiovascular parameters and measures of exertional dyspnea in patients with NSCLC. The primary limitation to exercise in patients with NSCLC appeared to be ventilatory limitation secondary to reductions in ventilatory capacity after pulmonary resection and may have also been due to greater ventilatory demand associated with peripheral deconditioning. Exercise tolerance was reduced in patients with NSCLC and was strongly correlated with diastolic

filling patterns at rest. In contrast to our hypothesis, we observed no evidence of neuromechanical uncoupling in the incremental or constant load exercise trials in patients with NSCLC. Ventilatory effort appeared to be well-matched to ventilatory output at any exercise intensity. The lack of association between any ventilatory parameters and exertional dyspnea in patients with NSCLC suggests that the mechanisms of exertional dyspnea are different than those previously identified in other respiratory diseases. Furthermore, we found no evidence to support our hypothesis that reduced diastolic filling and decreased left ventricular stroke volume would be associated with dyspnea and exercise intolerance in patients with NSCLC.

2.4.1 Exertional Dyspnea, Ventilatory and Gas Exchange Responses to Incremental Exercise

Maximal ratings of dyspnea intensity in patients with NSCLC were not significantly altered compared to controls, and were similar to those reported previously in healthy individuals and patients with other chronic respiratory conditions [36, 79, 80]. Patients with NSCLC therefore appear to curtail exercise at a similar level of dyspnea intensity in relation to control subjects. However, maximal ratings of dyspnea intensity were reported at a significantly lower peak absolute power output in patients with NSCLC, supporting that patients with NSCLC experience greater dyspnea at a comparable power output in relation to controls, especially as patients approach their peak exercise capacity.

The potential mechanisms responsible for this heightened dyspnea response in patients with NSCLC has not been previously studied. However, there are a number of factors associated with abnormal ventilatory patterns, changes in operating lung volumes and alterations in gas exchange following curative intent treatment for NSCLC which may contribute to exertional dyspnea in this population. After pulmonary resection, patients with NSCLC exhibited a relatively normal ventilatory response to incremental cycle exercise. However, patients with NSCLC reached maximal ventilation (V_E) at a significantly lower peak power output, which resulted in a leftward shift in the ventilatory

response compared to healthy controls. At any given submaximal workload, V_E was not found to be significantly higher in patients with NSCLC; however, V_E was seen to be significantly reduced at peak exercise in patients with NSCLC compared to controls. The lower V_E was accompanied by a comparable tidal volume response between patients with NSCLC and controls at submaximal exercise intensities, despite the controls being able to achieve a significantly greater tidal volume at maximal exercise. However, patients with NSCLC tended to have a higher breathing frequency throughout the exercise test, whereby breathing frequency tended to be increased for a given power output and was significantly increased above the levels of healthy controls at maximal exercise.

Patients with NSCLC have previously been shown to exhibit a blunted tidal volume response to incremental exercise after pulmonary resection, due to reductions in ventilatory capacity and static hyperinflation of the remaining lung parenchyma [20-23]. Reductions in total lung capacity (TLC) and forced vital capacity (FVC) after pulmonary resection impose mechanical constraints on the maximal ventilation that can be achieved during exercise and therefore constrain tidal volume expansion during exercise independent of the presence of any airway obstruction [19-23]. While augmented breathing frequency appears to compensate for impairments in tidal volume expansion at submaximal exercise intensities, patients with NSCLC are unable to reach maximal ventilations comparable to those observed in controls. This was evidenced by the extent of ventilatory limitation at exercise cessation in patients with NSCLC, whereby ventilatory reserve was notably reduced in patients with NSCLC at peak exercise in comparison to controls.

The blunted tidal volume response to incremental exercise in patients with NSCLC is similar to what has previously been observed in patients with COPD [68], despite being the result of distinct mechanisms in either condition. In patients with COPD, dynamic hyperinflation increases tidal breathing towards TLC, resulting in mechanical constraints on tidal volume expansion and a reduction in the ratio of tidal volume to vital capacity (V_T/VC) [68, 81]. A number of studies have demonstrated strong statistical correlations between the tidal volume response to exercise (V_T/IC ratio) and the extent of ventilatory limitation (V_E/MVC ratio) and ratings of exertional dyspnea in patients with COPD [36, 79]. In contrast, in this study there were no significant correlations between any of the ventilatory

parameters and dyspnea intensity in patients with NSCLC. Therefore, while the ventilatory pattern was altered in patients with NSCLC, it does not appear to be a key factor associated with exertional dyspnea in this population.

Changes in operational lung volumes have been shown to be primarily responsible for exertional dyspnea in patients with other chronic respiratory diseases, through changes in inspiratory muscle work associated with breathing at higher lung volumes [36, 75, 80, 82, 83]. Most notably, increases in end-expiratory lung volumes in patients COPD due to expiratory flow limitation and shortened expiratory time during exercise lead to tidal volume constraint and a significantly reduced inspiratory reserve volume (IRV). An IRV of <0.5 liters at maximal exercise has been identified as a critical point [83, 84] and is related to a sudden and sharp inflection in ratings of dyspnea intensity in patients with COPD. A similar finding has been observed in patients with interstitial lung disease (ILD) [80, 83] who also experience severe mechanical constraints on tidal volume expansion in the face of increased ventilatory demand during exercise. Operational lung volumes approach total lung capacity during exercise in patients with ILD due to substantial reductions in lung volumes associated with reduced lung compliance in this population. In this study, we similarly observed a significant reduction in IRV below a critical level in patients with NSCLC but not in controls. Interestingly, no significant differences in absolute end-inspiratory or end-expiratory lung volumes were observed between patients with NSCLC and healthy controls. However, when compared relative to TLC, patients with NSCLC were seen to operate at significantly higher lung volumes throughout exercise. This appeared to be independent of dynamic hyperinflation as there were no significant changes in EELV above resting levels. Instead, the reduced IRV was due to normal increases in EILV, which maintained tidal volume in the face of a reduced TLC. However, in contrast to the previous studies of O'Donnell et al. [36, 79, 83] we observed no significant correlations between the sensory intensity of dyspnea and any changes in operational lung volumes.

After pulmonary resection, patients with NSCLC may experience augmented ventilatory stimulation during exercise as a result of peripheral and respiratory muscle deconditioning [42, 85]. Resulting increases in efferent activation may act in combination with respiratory muscle weakness to

force patients to operate more closely to their $P_{I_{max}}$ [63-65]. We proposed that patients with NSCLC may also experience mechanical constraints on tidal volume expansion due to reductions in ventilatory capacity after pulmonary resection. This would result in an increased work of breathing which would further augment ventilatory stimulation during exercise. Similar to other chronic respiratory diseases, we proposed that this would result in a widening disparity between ventilatory effort ($P_{I_{insp}}/P_{I_{max}}$) and ventilatory output (V_T/V_C) during exercise in patients with NSCLC, and that this would be the primary contributing factor to exertional dyspnea in this population. To our knowledge, this is the first study to investigate neuromechanical uncoupling in patients with NSCLC. In contrast to our hypothesis and previous studies in patients with chronic respiratory disease, we found no evidence of neuromechanical uncoupling in patients with NSCLC even at maximal exercise. Specifically, ventilatory effort appeared to be well-matched to ventilatory output with a ratio of 0.5 at maximal exercise. Patients with NSCLC therefore achieved approximately two times the ventilatory output (tidal volume displacement) for a given ventilatory effort during exercise. The neuromechanical uncoupling response in patients with NSCLC more closely resembled that previously demonstrated in healthy individuals in contrast to those reported in patients with COPD, in whom the effort:displacement ratio is seen to exceed 1.0 even at rest [36, 80, 84, 86]. (The role of neuromechanical uncoupling in exertional dyspnea and exercise intolerance in patients with NSCLC is discussed further below).

Another factor that may contribute to exertional dyspnea in patients with chronic respiratory disease is gas exchange abnormalities that can reduce oxygen delivery and acutely alter the drive to breathe. We observed little evidence of gas exchange abnormalities among patients with NSCLC. Patients with NSCLC exhibited a significant reduction in the diffusing capacity for carbon monoxide (D_{LCO}) at rest. However, this difference disappeared after accounting for reductions in alveolar ventilation (V_A) after pulmonary resection. This is consistent with previous literature, which suggests that diffusing capacity is often high with respect to the extent of pulmonary resection due to recruitment of the remaining alveolar surface via static hyperinflation of the remaining lung parenchyma [20, 21, 29]. Oxyhemoglobin saturation (S_pO_2) was not different at rest compared to controls, but was found to be significantly reduced in patients with NSCLC during heavy and maximal

exercise. While the mean extent of hypoxemia was not of clinical relevance ($<5\%$ reduction in S_pO_2) reductions in S_pO_2 may be due to small increases in ventilation-perfusion mismatch or diffusion limitation after pulmonary resection (assuming that there are no differences in intrapulmonary or intracardiac shunt following resection). Interestingly, $P_{ET}O_2$ and $P_{ET}CO_2$ at end exercise were not significantly different compared to controls, suggesting that V_A was adequate even at maximal exercise. Similar results have been reported previously and demonstrate that the pattern of recruitment of the pulmonary capillary bed during exercise is normal after pulmonary resection, preventing the development of significant diffusion limitation and hypoxemia during exercise [29]. Furthermore, the level of hypoxemia observed during exercise was not related to exertional dyspnea in patients with NSCLC.

2.4.2 Exercise Limitation During Incremental Exercise in Patients with NSCLC

Exercise capacity was significantly reduced in patients with NSCLC compared to healthy controls. This was evidenced by a 16.5% relative reduction in peak oxygen uptake (VO_{2peak}) in the NSCLC group. The heart rate and mean blood pressure responses to exercise were normal in the NSCLC group; however, maximal heart rate was significantly reduced in comparison to control subjects. Furthermore, although a poor surrogate of stroke volume, O_2 pulse was not significantly reduced at maximal exercise in patients with NSCLC compared to controls, supporting that cardiac function is not the limiting factor to exercise in this population. In the majority of patients with NSCLC in the current study, the lower maximal heart rate was due to early cessation of exercise in the face of severe ventilatory limitation. More specifically, eight of the thirteen patients in the NSCLC group (62%) were primarily ventilatory limited ($V_{Epeak}/MVC > 85\%$) [74], while none of the control subjects were considered to be ventilatory limited. These findings are likely the result of reductions in ventilatory capacity and augmented ventilatory drive due to deconditioning associated with pulmonary resection. Consistent with previous literature, in all but one of the control subjects (89%) cardiovascular function was the limiting factor to exercise [87].

2.4.3 Exertional Dyspnea and Ventilatory Responses to Discontinuous Constant-Load Exercise

As expected, the ventilatory responses to constant load exercise were similar to what was observed in the incremental exercise test. Ventilatory parameters increased significantly with exercise intensity from rest to 75% W_{max} . Interestingly, while patients with NSCLC did not dynamically hyperinflate, we also observed no change in EELV with increasing exercise intensity. At rest, patients with NSCLC exhibited reduced expiratory muscle strength (MEP) compared to predicted values after pulmonary resection and we propose that this may have resulted in failure to reduce EELV during exercise. This is in contrast to what is commonly seen in healthy individuals, in whom expiratory muscle recruitment on expiration helps to prevent lung volumes from increasing towards the stiff portion of the lung compliance curve. Similar to the incremental exercise test, EELV increased significantly from rest to 75% W_{max} , resulting in a progressive reduction in inspiratory reserve volume (IRV). As depicted in Figure 2.13, the mean IRV at 75% W_{max} was approximately equal to the IRV measured at maximal exercise in the incremental exercise test. Once more, IRV was reduced below the critical value of 0.5 liters; however, we found no significant relationships between any ventilatory parameters or operational lung volumes and exertional dyspnea in patients with NSCLC [80, 82-84]. Moreover, patients with NSCLC appeared to report lower ratings of dyspnea intensity at 75% W_{max} compared to maximal exercise in the incremental exercise test, despite operating at the same lung volumes relative to total lung capacity. The relationship between changes in IRV and dyspnea intensity, in which the inflection in the tidal volume response marks the point where dyspnea intensity rises abruptly, has previously been shown to be maintained despite the exercise testing protocol (incremental or constant load) in patients with COPD [82]. This contrasting finding in NSCLC further supports that changes in operational lung volumes are not a key factor in governing exertional dyspnea experienced by patients with NSCLC after pulmonary resection, which is in vast contrast to other respiratory disease populations [80, 82-84].

Figure 2.13 Dyspnea intensity and IRV during incremental and constant load exercise in patients with NSCLC.

Abbreviations: IRV, inspiratory reserve volume.

Similar to the incremental exercise test, we found no evidence of neuromechanical uncoupling in patients with NSCLC during constant load exercise. In contrast to what has previously been found in patients with other chronic respiratory diseases, P_{insp} remained unchanged during exercise. Furthermore, inspiratory muscle strength (MIP) was found to be normal in patients with NSCLC, consistent with a previous study by Pelletier et al. [38]. Together, this resulted in a preserved $P_{\text{insp}}:P_{\text{Imax}}$ ratio during exercise. Neuromechanical uncoupling was therefore found to be unchanged throughout exercise, despite significant reductions in IRV, and actually tended to decrease at the onset of exercise, suggesting that patients are able to increase tidal volume without a noticeable increase in ventilatory effort.

Not surprisingly, we found no significant associations between neuromechanical uncoupling and ratings of dyspnea intensity or unpleasantness during exercise in patients with NSCLC. Taken together with our observations in the incremental exercise test, these findings further support that while neuromechanical uncoupling appears to be a principal mechanism of exertional dyspnea in patients with other chronic respiratory diseases [36, 79, 80], it does not appear to be a primary contributing factor to exertional dyspnea in patients with NSCLC after pulmonary resection.

We did, however, observe a significant increase in expiratory pressure (P_{exp}) from rest to 75% W_{max} . Furthermore, when we considered the tidal swing in pressure from P_{exp} to P_{insp} , we found a significant increase in the pressure differential from rest to 75% W_{max} . We therefore calculated a modified ratio of neuromechanical uncoupling (mNMU) which enabled us to consider inspiratory and expiratory effort together ($[P_{\text{exp}}-P_{\text{insp}}]/[P_{\text{Emax}}-P_{\text{Imax}}]$) in relation to the tidal volume response (V_T/VC). In this context, we did observe a small, albeit insignificant, increase in mNMU between the constant load exercise trials. While mNMU was not significantly related to ratings of dyspnea intensity or unpleasantness in the current study, we propose that a more inclusive measure may be a more important driver of dyspnea in this patient group and may warrant further investigation.

2.4.3.1 Sensory Qualities of Exertional Dyspnea in Patients with NSCLC

This is the first study to utilize the multidimensional dyspnea profile [61] to measure the sensory qualities of dyspnea in any cancer population. The primary sensations of exertional dyspnea reported by patients with NSCLC were the sensations of work / effort, unsatisfied inspiration or air hunger, and breathing rapidly and heavily. Patients with NSCLC did not report considerable mental effort to breathe or chest tightness. This is consistent with previous studies, which demonstrated that the sensation of chest tightness is unique to active bronchoconstriction in patients with asthma [58, 88]. In a previous study by O'Donnell et al. [36] the selection frequencies of qualitative descriptors of dyspnea related to perceived increases in the work, effort, and heaviness of breathing during exercise were found to be similar between healthy individuals and patients with chronic airflow limitation, suggesting that these symptoms may be non-discriminatory [36]. However, the sensation of unsatisfied inspiration was far more commonly reported in patients with chronic airflow limitation and was most strongly correlated with increases in the effort:displacement ratio during exercise. In the current study, we found no significant correlations between the sensory qualities of exertional dyspnea and any ventilatory parameters in patients with NSCLC, with the exception of a significant association between the sensation of work or effort and IRV at 75% $W_{\max}$ ($r^2 = 0.32$; $p = 0.05$). In patients with NSCLC, IRV was significantly reduced from rest to 75% $W_{\max}$ due to impaired ventilatory capacity and increased EILV during exercise. Therefore, while changes in operational lung volumes do not correlate with the intensity of exertional dyspnea, breathing close to TLC during higher intensity exercise appears to contribute to the increased sensation of work or effort to breathe in patients with NSCLC.

2.4.4 Exertional Dyspnea and Cardiovascular Responses to Discontinuous Constant-Load Exercise

This is the first study to utilize exercise echocardiography to investigate cardiovascular function in patients with NSCLC after pulmonary resection. We found no significant differences in

cardiac function between patients with NSCLC and control subjects at rest or during exercise. Patients with NSCLC exhibited a relatively normal response of heart rate and cardiac output to exercise. Furthermore, stroke volume was seen to increase significantly from rest to 25% W_{max} and then plateaued between 25% and 50% W_{max} , consistent with what has been previously reported in healthy aging [89]. Reductions in stroke volume have previously been suggested to be the result of impaired filling of the left ventricle secondary to a decreased pulmonary blood volume after pulmonary resection [27, 33]. Furthermore, both direct and indirect measurements of pulmonary artery systolic pressure (PASP) in patients with NSCLC have previously demonstrated significant increases in PASP after pulmonary resection due to reductions in the pulmonary vascular bed [27, 31, 32]. However, in the small number of patients where PASP could be measured ($n=5$) we observed relatively little evidence of elevated pulmonary artery systolic pressures (PASP) in patients with NSCLC at rest (PASP 29 ± 8 mmHg). The mechanism by which the stroke volume response to exercise is impaired is likely related to reductions in the pulmonary vascular bed associated with pulmonary resection which augments right ventricular afterload and reduces left ventricular filling via series and/or direct ventricular interaction [20].

Patients with NSCLC demonstrated an increased use of preload from rest to 25% W_{max} , likely due to increased venous return associated with the respiratory and skeletal muscle pumps at the start of exercise [90]. There was no significant change in end-systolic volume (ESV) between the constant load exercise trials. Patients with NSCLC exhibited similar reductions in total peripheral resistance (TPR) to control subjects, with reductions in TPR of 58% and 47% from rest to 75% W_{max} , respectively. While not statistically different, EDV and SV were 12% and 18% lower, respectively, at 75% W_{max} in patients with NSCLC compared to control subjects. Additionally, due to the greater body surface area in the NSCLC group, when scaled allometrically to body surface area EDV and SV were 28% and 26% lower, respectively, at 75% W_{max} in the NSCLC group. The lack of statistical significance in these results was likely due to the small sample size and the large interindividual differences observed in the NSCLC group. In relation to dyspnea, we found no significant associations between any of the cardiac parameters and the sensory intensity or unpleasantness of dyspnea in patients with NSCLC. We did, however, find significant associations between the ratio of

unpleasantness to sensory intensity (A1/SI) and cardiac output, both at 75% $W_{\max}$ and the change score from rest to 75% $W_{\max}$. The A1/SI ratio was significantly increased during moderate and heavy exercise in patients with NSCLC, indicating that patients tended to perceive greater unpleasantness for a given sensory intensity at increased exercise intensities. This may have been due to reduced oxygen delivery to the exercising muscles, evidenced by a tendency towards a lower cardiac output during exercise compared to controls, and may have lead to earlier metabolic acidosis and augmented ventilatory drive in patients with NSCLC.

2.4.5 Exertional Dyspnea and Exercise Tolerance in Patients with NSCLC

We undertook a constant load exercise trial to symptom limitation in patients with NSCLC to further investigate the potential mechanisms of exertional dyspnea and exercise intolerance in this patient group. Cardiopulmonary responses were similar to those previously discussed in the incremental and constant load exercise trials. Cardiopulmonary parameters were examined at an isotime during exercise where we collected echocardiographic measurements after the obtainment of steady state to investigate the relationships between cardiopulmonary responses to exercise and measures of exertional dyspnea and exercise tolerance. We found no significant associations between any ventilatory or cardiovascular parameters and either exertional dyspnea or exercise tolerance in patients with NSCLC, with the exception of a significant correlation between the resting E/A ratio and exercise tolerance ($r^2 = 0.58$; $p = 0.035$). Such that those with the lowest E/A ratio (i.e. those more reliant on late atrial contraction) had the most attenuated exercise tolerance. This finding is consistent with previous studies in patients with congestive heart failure and patients with COPD [91, 92], and indicates that those with the poorest diastolic filling patterns at rest exhibit the greatest exercise intolerance, likely through the inability to enhance EDV and utilize the Frank-Starling mechanism.

Similar to the incremental exercise test, patients with NSCLC experienced significantly greater reductions in ventilatory reserve (V_E/MVC) during the constant load trial compared to controls.

Despite this, patients with NSCLC did not appear to develop considerable ventilatory constraint during the constant load exercise trial (V_E/MVC $68 \pm 20\%$ at $75\% W_{max}$). Furthermore, half of the patients who completed the constant load exercise trial to symptom limitation were neither ventilatory nor cardiac limited at end exercise. In all but one of these patients, leg discomfort was cited as the primary reason for ending exercise, supporting that peripheral muscle deconditioning related to surgical intervention and disease lifestyle may be a primary contributing factor to exercise intolerance in patients with NSCLC.

2.4.6 Potential Mechanisms of Exertional Dyspnea in Patients with NSCLC

When asked the reason for stopping exercise, the majority of patients cited leg discomfort, either alone or in combination with shortness of breath. This is consistent with what has previously been shown in healthy aging populations. Exercise intolerance in patients with NSCLC after pulmonary resection may therefore be the result of respiratory and/or peripheral muscle weakness secondary to deconditioning in the perioperative period. We observed reductions in expiratory muscle strength compared to predicted values in the current sample of patients with NSCLC. Furthermore, patients with NSCLC achieved a significantly lower power output in the incremental exercise test compared to control subjects, which may have been due in part to peripheral muscle deconditioning. In the face of reduced vital capacity and increased ventilatory constraint after pulmonary resection, earlier metabolic acidosis and ventilatory stimulation secondary to deconditioning may lead to increased dyspnea and earlier exercise curtailment in patients with NSCLC. Exercise interventions designed to improve respiratory and peripheral muscle function in patients with NSCLC after pulmonary resection may therefore be effective in reducing exertional dyspnea and improving exercise tolerance in this population.

2.4.7 Clinical Relevance

After pulmonary resection, patients with NSCLC experience reduced exercise tolerance, as demonstrated by the significant reduction in $\text{VO}_{2\text{peak}}$ compared to control subjects in the present study. Patients with NSCLC also reported increased intensity of dyspnea at lower levels of power output and ventilation close to maximal exercise relative to control subjects. Ventilatory patterns appeared to be altered in patients with NSCLC but were not clearly related to either the dyspnea response or the reduction in $\text{VO}_{2\text{peak}}$. Therefore, the primary limitation to exercise in patients with NSCLC after pulmonary resection may be related simply to respiratory and/or peripheral muscle deconditioning secondary to surgical intervention or disease lifestyle. Augmented central motor output, in response to altered afferent inputs to the sensory cortex, is strongly related to dyspnea in patients with other chronic respiratory diseases [83, 93]. Changes in the balance between ventilatory demand and capacity following curative intent treatment for NSCLC may lead to increased inspiratory neural drive, similar to what has been reported in other chronic respiratory disease populations [83, 93], and may be associated with exertional dyspnea and earlier exercise curtailment in patients with NSCLC. Previous studies have demonstrated the efficacy of exercise training programs to improve functional capacity and to reduce mortality risk in patients with NSCLC [45, 94]. Therapeutic interventions designed to improve respiratory and/or peripheral muscle function may therefore be effective in reducing the limitation to exercise in this population independent of the fact that ventilatory capacity is reduced after pulmonary resection.

2.5 Summary

This is the first study to comprehensively examine cardiopulmonary responses to exercise in patients with NSCLC after pulmonary resection. Additionally, this is the first study to utilize the multidimensional dyspnea profile to measure the immediate affective and sensory dimensions of dyspnea in patients with NSCLC. We hypothesized that greater neuromechanical uncoupling would be the principal mechanism of dyspnea in patients with NSCLC, and that neuromechanical

uncoupling would be associated with exercise intolerance in patients with NSCLC. While patients with NSCLC exhibited increased exertional dyspnea at lower levels of power output and ventilation compared to healthy controls, dyspnea was not found to be associated with any of the ventilatory parameters, including neuromechanical uncoupling. Moreover, cardiovascular function was similar to that observed in healthy aging and we found no significant associations between dyspnea or exercise tolerance and any of the cardiovascular parameters. The primary limitation to exercise in our sample of patients with NSCLC after pulmonary resection appeared to be ventilatory constraint due to reduced ventilatory capacity and augmented ventilatory drive secondary to deconditioning in the perioperative period. Exercise interventions designed to improve respiratory and peripheral muscle function in patients with NSCLC after pulmonary resection may therefore be effective in reducing exertional dyspnea and improving HRQOL in this population.

Chapter 3 Extended Discussion

Shortness of breath is the most common cause of emergency department visits among all cardiopulmonary diagnoses [47]. It has a profound negative impact on HRQOL and is an independent predictor of mortality in patients with NSCLC [35, 48]. Dyspnea is associated with increased levels of depression, anxiety, and reduced levels of physical functioning [37]. The emotional influence of dyspnea undermines self-confidence among patients in being able to perform physical activity, resulting in premature cessation of exercise and exercise avoidance [34, 45]. Such limitations impair the capacity for patients to perform activities of daily living and leads to additional loss of functional independence, which further increases mortality risk [39, 49].

Shortness of breath is the most prevalent symptom experienced by patients after curative intent treatment for NSCLC [34, 35]. Over 20% of patients present with dyspnea at the time of diagnosis, however, the incidence of dyspnea has been shown to increase 3-fold after pulmonary resection [37]. Furthermore, dyspnea persists for several years post-surgery and remains elevated compared to preoperative levels [34, 37].

It has become increasingly well-recognized that dyspnea is a multidimensional symptom, comprised of qualitatively distinct sensations that have both sensory and affective dimensions which act to govern its intensity and unpleasantness as perceived by the patient [47]. This is the first study to employ the Multidimensional Dyspnea Profile (MDP), previously developed by Banzett et al. [61], to provide a comprehensive assessment of the affective and sensory dimensions of dyspnea as well as the sensory qualities of dyspnea in patients with NSCLC.

The mechanisms responsible for dyspnea in cancer patients remain considerably understudied. Due to its multifactorial nature, there are many factors which likely contribute to the overall intensity and unpleasantness of the symptom. Independent of the physiological mechanisms, additional factors including: the primary site of cancer, stage, therapies received, age, sex, fitness level and underlying comorbidities likely also contribute. This study attempted to conduct a

preliminary examination into the potential mechanisms of exertional dyspnea in postsurgical patients with NSCLC. We examined a variety of systems, including the respiratory and cardiovascular systems, in an attempt to identify the primary factors contributing to exertional dyspnea in this population, understanding that dyspnea is commonly a multifactorial symptom.

Thirteen patients who had previously undergone pulmonary resection for NSCLC were recruited and performed the study. Disease stages among patients included stages IA (54%), IB (23%), IIB (15%) and IIIA (8%). The majority of patients (62%) underwent lobectomy of the right upper (39%), left upper (15%) or left lower (8%) lobes. Three patients (23%) underwent wedge resection of the right upper, left upper or right lower lobes. Finally, two patients (15%) underwent pneumonectomy of the left lung. Six patients (46%) underwent thoracotomy, while the remaining seven patients (54%) underwent video-assisted thoracoscopic surgery. Mean time from surgery was 2.5 ± 1.9 years and ranged from 5.5 months to 5.7 years. Adjuvant therapies included chemoradiotherapy in one patient and chemotherapy alone in an additional four patients. The minimum time elapsed from therapy to the time of inclusion was 9.7 weeks. Concomitant comorbidities included chronic obstructive pulmonary disease (COPD) (38%), hypertension (31%), hypercholesteremia (15%), major depressive disorder (15%) and bipolar disorder (8%). As such, the lack of statistical significance in our findings was likely influenced by the clear heterogeneity of our sample and the considerable variation in disease presentation, therapies received and comorbidities. However, the finding that neuromechanical uncoupling was essentially normal (i.e. ventilatory effort was well-matched to ventilatory output) throughout each different form of exercise, as discussed in the previous chapter, suggests that neuromechanical uncoupling is not a primary mechanism of exertional dyspnea in patients with NSCLC. Furthermore, due to the considerable heterogeneity in our sample, it cannot be ruled out that the mechanisms of exertional dyspnea may vary from individual-to-individual and one primary mechanism may not exist in patients with NSCLC.

It has become increasingly well-accepted over the last decade that chronic obstructive pulmonary disease (COPD) is an independent risk factor for NSCLC, independent of smoking status [95]. Therefore, the proportion of patients in our sample presenting with concomitant COPD (38%) is

not surprising and is consistent with previous research in this population. An interesting element of the current study, which we did not initially set out to investigate, was the potentially additive effect of concomitant COPD on exertional dyspnea in patients with NSCLC. We therefore undertook a preliminary subgroup analysis in which we divided those patients with concomitant COPD from those with NSCLC alone. Additionally, we utilized the extensive COPD data available in our laboratory to closely match patients for age, sex, height, weight and disease severity (FEV₁) to create a COPD comparison group (see Table 3.1 Subgroup Characteristics).

Table 3.1 Subgroup Characteristics

	Control (n=9)	NSCLC (n=8)	COPD (n=5)	NSCLC + COPD (n=5)
Male:Female	3:6 (33)	1:7 (13)	2:3 (40)	2:3 (40)
Age, yr	64 ± 6	67 ± 10	69 ± 5	69 ± 8
Weight, kg	66 ± 8	80 ± 17	67 ± 11	73 ± 14
BMI, kg/m ²	25 ± 2	28 ± 6	24 ± 2	28 ± 6
FEV ₁ , L	3.06 ± 0.64	1.93 ± 0.62	1.09 ± 0.23	0.99 ± 0.26
% predicted	120 ± 16	77 ± 23	44 ± 2	43 ± 2
FVC, L	4.00 ± 0.93	3.12 ± 0.79	3.12 ± 0.77	2.83 ± 0.78
% predicted	124 ± 15	97 ± 20	98 ± 9	96 ± 17
FEV ₁ /FVC, %	77 ± 5	61 ± 8	35 ± 3	35 ± 8
Power Output, W	104 ± 32	90 ± 26	66 ± 17	54 ± 17
% predicted	92 ± 8	81 ± 18	59 ± 22	54 ± 8
VO _{2peak} , ml·kg ⁻¹ ·min ⁻¹	22.7 ± 3.8	19.4 ± 3.4	14.6 ± 2.6	13.5 ± 3.7
% predicted	97 ± 9	93 ± 16	65 ± 15	62 ± 4

Values are no. (%) or means ± SD. *Abbreviations:* BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; VO_{2peak}, peak oxygen consumption.

The incremental exercise responses in the four groups are depicted in Figure 3.1. Similar to what was reported in chapter two, patients with NSCLC alone curtail exercise at a similar intensity of dyspnea relative to controls. However, maximal ratings of dyspnea intensity occur at a significantly lower peak power output, which supports that dyspnea is increased earlier in exercise in patients with NSCLC and no other respiratory comorbidities and likely explains why more patients with NSCLC report dyspnea with exertion on clinical presentation [37]. Patients with COPD exhibit greater dyspnea for any given power output compared to patients with NSCLC. This relationship appears to be shifted further up and to the left when NSCLC is combined with COPD, compared to either the NSCLC or COPD groups alone. The mechanisms of exertional dyspnea in patients with COPD may therefore be further exacerbated by the consequences of lung cancer especially following surgical intervention.

Figure 3.1 Cardiopulmonary responses to incremental exercise in patients with NSCLC, COPD, NSCLC + COPD, and controls.

NSCLC (n=8); COPD (n=5); NSCLC + COPD (n=5); controls (n=9). *Abbreviations:* TLC, total lung capacity; IRV, inspiratory reserve volume; SpO_2 , oxyhemoglobin saturation. End-inspiratory and end-expiratory lung volumes in panel 5 are denoted by dotted and solid lines, respectively.

Consistent with the mechanisms previously discussed in both patient groups, patients with combined NSCLC and COPD appear to operate at higher lung volumes closer to their total lung capacity. End inspiratory and expiratory lung volumes appeared to be significantly elevated in those patients with concomitant COPD and more closely resembled the lung volumes exhibited in patients with COPD in comparison to those with NSCLC alone. We propose that this is due to the combined effects of reduced ventilatory capacity and dynamic hyperinflation during exercise. Consequently, patients with combined NSCLC and COPD experienced the greatest decline in inspiratory reserve volume (IRV). Consistent with previous research [83, 84], once IRV went beyond a critical point there was a steep increase in exertional dyspnea in patients with COPD alone and those with combined NSCLC and COPD. However, this was not the case in healthy individuals or in patients with NSCLC alone. Interestingly, the mean FEV_1/FVC ratio was 0.61 ± 0.08 in the NSCLC group after the removal of those with clinically diagnosed COPD, suggesting that some individuals in the NSCLC group still have fixed airway obstruction. In fact, six out of the eight individuals had an FEV_1/FVC ratio < 0.70 and an FEV_1/FVC ratio below the lower limit of normal. This discrepancy in the response between critical IRV and dyspnea supports our contention that the mechanisms of dyspnea are different between NSCLC and COPD, but also raise questions regarding whether this is a “critical” relationship or an epiphenomena in COPD.

As ventilatory demands increase during exercise, reductions in ventilatory capacity after pulmonary resection may further constrain tidal volume expansion in patients with concomitant COPD. This is evidenced by a blunted tidal volume response to incremental exercise in patients with combined NSCLC and COPD (Figure 3.1). Furthermore, respiratory and/or peripheral muscle deconditioning secondary to curative intent treatment or disease lifestyle may result in earlier metabolic acidosis and ventilatory stimulation and may contribute to increased dyspnea and earlier exercise curtailment in patients with combined NSCLC and COPD.

Alveolar dead space volume is increased in patients with COPD due to degradation of the lung parenchyma and resultant airway collapse. Dead space ventilation is further augmented during exercise as dynamic hyperinflation develops and patients are forced to adopt a more rapid and

shallow breathing pattern. We see a similar response in patients with NSCLC after pulmonary resection due to declines in ventilatory capacity. This results in a corresponding leftward shift of the ventilation response curve, consistent with what we see in Figure 3.1. This response appears to be greatest in patients with combined NSCLC and COPD, in whom altered lung mechanics and surgical resection may further compromise ventilatory reserve during exercise.

Augmented dead space ventilation in patients with COPD during exercise is related to increased ventilation-perfusion (V_A/Q) mismatch and alveolar hypoventilation and resulting gas exchange abnormalities. Greater reductions in oxyhemoglobin saturation (S_pO_2) were observed in both of the COPD groups compared to those with NSCLC alone (Figure 3.1). As our patients with concomitant COPD have severe disease, as evidenced by the FEV_1 (Table 3.1), hypoxemia likely occurs due to V_A/Q mismatch, diffusion limitation and alveolar hypoventilation which may have further contributed to the greater dyspnea response observed in these patients.

The results of this preliminary subgroup analysis suggest that postsurgical patients with NSCLC experience altered ventilatory mechanics and elevated exertional dyspnea irrespective of the effects of concomitant COPD. However, when combined with the physiological consequences of COPD, pulmonary resection for NSCLC appears to have an additive effect on the prevailing cardiopulmonary responses and exertional dyspnea in this population, likely resulting from the interaction of multiple mechanisms that contribute to exertional dyspnea in patients with either of these chronic respiratory conditions.

3.1 Study Limitations

This is the first study to explore the major factors contributing to exertional dyspnea in postsurgical patients with NSCLC. The current study was designed to generate data, which could be utilized to power a much larger clinical study to identify the mechanisms associated with exertional dyspnea in this population. As such the results are of a preliminary nature and are limited by the small cohort included in our current analysis. No study has previously investigated the mechanisms of

dyspnea in patients with NSCLC or the role of neuromechanical uncoupling as a potential mechanism of dyspnea in this population. As such, a power calculation could not be performed for this preliminary study. Due to the level of heterogeneity previously discussed in our current sample and the large variance observed in our population, we realize we are underpowered to detect some of the potential correlates of exertional dyspnea examined in our study. Despite this, we find that the current study provides important information to guide our future studies in this area. Understanding that “association is not mechanism”, the data collected from this study will help us to design more focused trials that target specific mechanisms of dyspnea in postsurgical patients with NSCLC.

We examined exercise responses at relative intensities (i.e. % W_{max}) due to the considerable heterogeneity in absolute workload. As some patients with COPD or those after pulmonary resection may be ventilatory limited below ventilatory threshold, relative workload may be a considerably different stressor between patients. However, the utilization of an absolute workload was not possible as it would have to be set to the minimum intensity for the most limited patient, which cannot be done with a rolling recruitment approach such as the one employed in the current study.

To our knowledge, this is the first study to measure lung mechanics in patients with NSCLC. We experienced considerably greater difficulties associated with the esophageal balloon catheter than in our previous work in patients with other chronic respiratory conditions. A number of patients expressed anxiety around passing any object into the throat. Two patients declined to consent for participation due to inclusion of the esophageal balloon catheter. Patients expressed anxiety after having previously undergone endobronchial biopsy procedures or tracheotomy. Multiple patients described experiencing prolonged negative side effects after undergoing bronchoscopy. These included abnormal voice changes (e.g. hoarseness) and muscle tension dysphonia. In those who consented to insertion of the esophageal balloon catheter, we experienced considerable difficulties during insertion in a number of patients potentially due to remodeling of the sinuses and upper airway due to age, chronic smoking, inflammatory respiratory disease, and the potential effects of surgery. Esophageal pressures were successfully measured in seven patients. Of the remaining six patients, three patients declined insertion of the esophageal balloon catheter on arrival, two patients

experienced uncontrollable cough during introduction of the esophageal balloon, and the esophageal balloon was retracted from one patient due to irritation and pain resulting from scar tissue associated with a previous tracheotomy. Consequently, a larger sample size is needed to enable the collection of considerably more mechanics data in this population.

Finally, this is the first study to conduct echocardiography during exercise in patients with NSCLC. Exercise echocardiography poses a number of significant challenges even in healthy populations. We therefore tried to recruit patients with an acceptable echocardiographic window and exclude patients and data when acceptable echocardiogram quality could not be obtained. With exercise, movement, increases in ventilation, and increases in lung volume associated with disease offer additional challenges as the inflated lung is a very poor medium for sound waves. Additionally, extensive pulmonary resection was found to alter traditional cardiac anatomy, which posed further difficulties in some participants. As such, we realize that there is considerable variability in the cardiac data obtained and that a larger sample size is needed to effectively understand the cardiac responses to exercise in this population.

3.2 Future Directions

Patients with NSCLC exhibit significant reductions in ventilatory capacity after pulmonary resection; however, the effects of reduced ventilatory reserve on changes in dyspnea from before to after surgery are unknown. Future studies should aim to examine how dyspnea and exercise intolerance are altered after pulmonary resection with short- and long-term comparisons to presurgical measures to understand the immediate and long-term consequences of pulmonary resection on changes in dyspnea and exercise tolerance in patients with NSCLC.

The primary limitation to exercise in patients with NSCLC appeared to be ventilatory limitation secondary to reductions in ventilatory capacity after pulmonary resection. This may have also been due to greater ventilatory demand associated with peripheral deconditioning. Exercise interventions designed to improve respiratory and peripheral muscle function in patients with NSCLC after

pulmonary resection may therefore be effective in reducing exertional dyspnea and improving exercise tolerance in this population. It is well-accepted that exercise and respiratory muscle training programs are commonly associated with reductions in dyspnea and improved exercise tolerance and HRQOL in patients with other chronic respiratory conditions. However, there is currently no formal exercise rehabilitation available for patients with NSCLC and this provides an exciting avenue for the development of a tailored exercise training program which may be beneficial for improving HRQOL in patients with NSCLC.

3.3 Conclusion

Patients with NSCLC exhibit increased exertional dyspnea at lower workloads and ventilation in comparison to control subjects. However, dyspnea was not found to be associated with any of the ventilatory parameters examined, including neuromechanical uncoupling which we hypothesized would be the principal mechanism of exertional dyspnea in patients with NSCLC after pulmonary resection. Moreover, cardiovascular function was similar to that observed in healthy aging and we found no significant associations between dyspnea or exercise tolerance and any of the cardiovascular parameters. We propose that respiratory and peripheral muscle deconditioning secondary to surgical intervention or disease lifestyle may lead to an imbalance between ventilatory demand and capacity which may contribute to exertional dyspnea in this population. Patients with NSCLC may experience increased ventilatory drive in response to disease-specific afferent inputs to the sensory cortex which lead to exertional dyspnea and earlier exercise curtailment, similar to what has been reported in patients with other chronic respiratory disease populations [83, 93]. Furthermore, the primary limitation to exercise in our sample of patients with NSCLC after pulmonary resection appeared to be ventilatory constraint in the presence of reduced ventilatory capacity and augmented ventilatory stimulation secondary to deconditioning in the perioperative period. Larger studies are necessary to overcome the substantial heterogeneity among patients with NSCLC observed in this preliminary study to further delineate the mechanisms of exertional dyspnea and exercise intolerance in this population. An improved understanding of the mechanisms responsible for

dyspnea in patients with NSCLC will help to enable the development of therapeutic interventions, with the ultimate aim of reducing dyspnea and improving HRQOL in this population.

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Appendices

Appendix A: Informed Consent

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PARTICIPANT INFORMATION AND CONSENT FORM

Title of Project: Mechanisms of Exertional Dyspnea in Postsurgical Patients with Non-Small Cell Lung Cancer

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INTRODUCTION

You are being invited to take part in this research study because you have undergone a lung resection for non-small cell lung cancer.

YOUR PARTICIPATION IS VOLUNTARY

Your participation is entirely voluntary. You have the right to refuse to participate in this study. If you decide to participate, you may still choose to withdraw from the study at any time without any negative consequences to the medical care, education, or other services to which you are entitled or are presently receiving. You do not have to give any reason for your decision. Before you decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what will happen to you during the study and the possible benefits, risks and discomforts. If you wish to participate in this study, you will be asked to sign this form. Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

BACKGROUND

Many patients who have undergone a lung resection for non-small cell lung cancer notice that they become short of breath when they exert themselves physically. Shortness of breath upon exertion is more common among lung cancer patients than in any other cancer. The reasons responsible for why you may feel short of breath during exercise are not well understood. There is some evidence to suggest that the muscles you use to breathe are weakened which may contribute to this unpleasant sensation. For this reason, even when the breathing muscles are working hard, they may have difficulty moving enough air in and out of the lungs. We believe that it is this 'mismatch' between the amount of work your breathing muscles are doing and the amount of air they are able to move in and out of your lungs that is responsible for the shortness of breath you experience.

It is the aim of this study to investigate what the major factors contributing to your shortness of breath are, and how your shortness of breath influences your ability to exercise. This study is a pilot study which means that it is a small-scale preliminary study, in our case with 20 participants, designed to explore the causes of shortness of breath in patients with your condition.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to explore the factors which may contribute to your shortness of breath, and to see how shortness of breath limits your ability to exercise. Understanding the mechanisms and

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the contributing factors behind shortness of breath and exercise intolerance in patients following lung resection will help us to develop therapies to help patients with your condition.

WHO CAN PARTICIPATE IN THIS STUDY?

If it has been more than 3 months since your lung resection and your condition has been stable, with no ongoing reversible problems, for the last 6 weeks (i.e. you have not had a change in your condition or been admitted to the hospital in the last 6 weeks) then you may be eligible to participate in the study.

WHO SHOULD NOT PARTICIPATE IN THIS STUDY?

If you have had a change in your condition or have been admitted to hospital in the last 6 weeks you should not participate in the study until you have returned to your previous condition for at least 6 weeks. If you have heart problems that limit your ability to exercise or suffer from pain in your muscles and joints with exercise you should also not take part. Additionally, we will exclude individuals who have greatly reduced blood oxygen levels during exercise, have uncontrolled high blood pressure, have diabetes, or have a body mass index (the ratio of your height:weight) above 35 kg/m². It is required that we are able to obtain quality echocardiographic images of your heart for this study, therefore if we are unable to do so you may be excluded. Furthermore, individuals who are unable to understand and sign the consent for participation in this study will be excluded.

WHAT DOES THE STUDY INVOLVE?

You will need to come to the Kelowna General Hospital on one occasion for a period of 3-4 hours.

During this visit, you will perform a breathing test (pulmonary function test) and an incremental exercise test on a stationary bicycle. During this exercise test we will also assess whether or not we can get a clear picture of your heart using an ultrasound machine. After one hour of rest, you will perform an exercise test at three different intensities (one easy, one moderate, and one somewhat hard). During this final exercise test, the pressures that your breathing muscles generate to breathe will be measured and ultrasound images of the heart will be obtained.

Specific Procedures

If you agree to take part in this study, the procedures you can expect will include the following:

(1) Pulmonary Function Test

What is this? This test is similar to those you have performed on a regular basis to monitor your condition. You will sit in a comfortable chair in a large clear chamber and breathe through a

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mouthpiece while wearing a nose clip. You will be asked to breathe normally and sometimes you will inhale all the way and exhale all the way as fast as you can. After the initial test is performed you will be given a bronchodilator medication (**bronchodilators are given by inhalation [with a puffer] to open or relax the breathing tubes or airways**) to be sure that your airways are fully open. The bronchodilator you will be given is called Ventolin and you will be given up to four puffs (400 µg) of the medication. The breathing test will then be repeated.

Time commitment: 45 minutes

Why is this important? The breathing test (spirometry) will be done to measure your lung function (how strong your lungs are).

(2) Incremental Exercise Test

What is this test? This test is an exercise test that starts easy and slowly gets harder until you feel like you cannot keep exercising due to either shortness of breath or leg discomfort. This test will be done on a stationary bicycle and you will breathe through a mouthpiece while wearing a nose clip to collect your expired air. The pressure produced while you breathe will be measured using a balloon catheter (see 'measurements of respiratory pressures' below). During this exercise test we will assess whether or not we can get a clear picture of your heart using an ultrasound machine. Small stickers (electrodes) will also be stuck to your chest so that we can monitor your heart during the test.

Time commitment: 45 minutes (only exercising for 10-12 minutes)

3) Discontinuous Exercise Test

What is this test? This test is an exercise test that remains at a constant workload of easy, moderate and somewhat hard. Rest is given between each work segment. On the final exercise segment (somewhat hard), you will exercise at a constant workload until you get too tired or too short of breath to keep exercising. This test will be done on a stationary bicycle and you will breathe through a mouthpiece while wearing a nose clip to collect your expired air. Small stickers (electrodes) will also be stuck to your chest so that we can monitor your heart during the test.

Time commitment: 1-1.5 hours (only exercising for ~5-10 minutes for each of the three exercise bouts)

Measurements to be made during the discontinuous exercise test:

- **Echocardiogram (Heart Ultrasound)**

What is this? This is an ultrasound picture taken of the heart. It is a very similar procedure to that done to get a picture of an unborn baby. A gel will be placed on your chest and then a small device that emits sound waves will be placed on the gel to get a picture of your heart. There are no risks associated with this procedure.

- **Measurements of Respiratory Pressures**

What is this? In order to measure the pressure produced while you breathe we will insert a small balloon through your nose so that it sits in your esophagus (food pipe). Upon arriving at the lab you will sit in a comfortable chair and the back of your nose and throat will be sprayed

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with a local anaesthetic called Lidocaine (similar to the anaesthetic used when you have dental work). Routinely, three sprays (30 mg) of Lidocaine will be given at the back of your nose and throat. A balloon catheter, which is like a thin piece of spaghetti, will then be passed through your nostril and nasal cavity towards the back of your throat. You will then swallow the balloon catheter into your stomach by sipping water through a straw. The catheter will then be pulled back approximately 10 cm and positioned in the lower third of your esophagus (food pipe). A small piece of tape will be attached to your nose and cheek to hold the catheter in place. The balloon will not interfere while you exercise and will not obstruct breathing. The balloon will remain in for both exercise tests and will be removed immediately after the second exercise test.

HOW WILL DATA BE STORED?

Study data will be stored in a secure location accessible only to the study investigators. Any hard copy data will be stored in a locked filing cabinet, while all electronic data will be stored in a firewall, password and encryption protected computer. Data will be stored for 12 years after completion of the study.

WHAT ARE THE RISKS?

The exercise that you will be performing is regarded as safe. All testing will be performed under appropriate supervision and appropriate resuscitation equipment will be available. Stress test data from other investigations, suggest that the likelihood of dying from sudden cardiac death is 5 per 100,000 tests. This usually only occurs in people who already have some form of heart disease.

You will be closely monitored throughout the protocol and a physician will be available in the vicinity of the pulmonary function laboratory if required during the incremental exercise test. In the case of an unexpected cardiac event, the KGH emergency team will be called immediately and a full resuscitation cart is available. You will be taken to the Emergency Department at Kelowna General Hospital which is ~200m away from the pulmonary function laboratory.

Following all of the exercise sessions you may experience muscle soreness, which will disappear within a few days. The balloon catheter may cause discomfort on insertion, nosebleed, gagging, or vomiting. There is also a small risk that you might be allergic to the local anesthetic used (Lidocaine, 30 mg). ***Please inform the investigator*** if you know that you have such an allergy. During the lung function testing you will be administered a medication called Ventolin (you will be given up to four puffs or 400 µg) which may cause tremor, nervousness, or palpitations (and possibly cough/throat irritation). You would have received this medication when you have performed this test previously and may be prescribed the same drug as a rescue medication.

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WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

If you agree to participate in this study there may not be a direct medical benefit to you. However, you will get an up to date pulmonary function assessment, your current fitness level will be evaluated, and you will be told how your lungs and heart are functioning at rest and during exercise. The information we get from this study may help us to provide better treatments in the future for patients recovering from lung resection for NSCLC as it will allow us to better understand the mechanisms of shortness of breath and their influence on exercise intolerance.

WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE?

Participation in this study is entirely voluntary. You may refuse to participate or you may withdraw from the study at any time without prejudice. If you decide to withdraw from the study, there will be no penalty or loss of benefits to which you are otherwise entitled, and your future medical care will not be affected. You do not waive any of your rights by signing this consent form.

The study doctor(s)/investigators may decide to discontinue the study at any time, or withdraw you from the study at any time, if they feel that it is in your best interests.

If you choose to enter the study and then decide to withdraw at a later time, all data collected about you during your enrolment in the study will be retained for analysis. By law, this data cannot be destroyed.

CONFIDENTIALITY

Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of the UBC Clinical Research Ethics Board for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

You will be assigned a unique study number as a participant in this study. This number will not include any personal information that could identify you (e.g., it will not include your Personal Health Number, SIN, or your initials, etc.). Only this number will be used on any research related information collected about you during the course of this study, so that your identity will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

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Your rights to privacy are legally protected by federal and provincial laws that require safeguards to insure that your privacy is respected. You also have the legal right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

WHAT HAPPENS IF SOMETHING GOES WRONG?

By signing this form, you do not give up any of your legal rights and you do not release the study doctor, participating institutions, or anyone else from their legal and professional duties. If you become ill or physically injured as a result of participation in this study, medical treatment will be provided at no additional cost to you. The costs of your medical treatment will be paid by your provincial medical plan and/or by the study sponsor.

WHAT WILL THE STUDY COST ME?

You will be reimbursed for any parking expenses that you incur while participating in the study. If you would like to be reimbursed please provide your parking receipts to the study investigators.

WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION?

A researcher will be available on every occasion to explain the procedure and to answer any questions. If you have any other questions or desire further information about this study before or during participation, you can contact Dr. Neil Eves via e-mail (neil.eves@ubc.ca) or phone (250-807-9676), or Ms. Megan Harper via e-mail (megan.harper@ubc.ca) or phone (250-807-8860).

WHO DO I CONTACT IF I HAVE ANY QUESTIONS OR CONCERNS ABOUT MY RIGHTS AS A SUBJECT DURING THE STUDY?

If you have any concerns or complaints about your rights as a research participant and/or your experiences while participating in this study, contact the Research Participant Complaint Line in the University of British Columbia Office of Research Services by e-mail at RSIL@ors.ubc.ca or by phone at 604-822-8598 (Toll Free: 1-877-822-8598).

If you have questions about your rights as a research participant, you may contact the Chair of the Interior Health Research Ethics Board by phone at (250) 870-4602 or by email to researchethics@interiorhealth.ca.

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Mechanisms of Exertional Dyspnea in Postsurgical Patients with Non-Small Cell Lung Cancer

PARTICIPANT CONSENT TO PARTICIPATE

My signature on this consent form means:

- I have read and understood the participant information and consent form.
- I have had sufficient time to consider the information provided and to ask for advice if necessary.
- I have had the opportunity to ask questions and have had satisfactory responses to my questions.
- I understand that all of the information collected will be kept confidential and that the results will only be used for scientific objectives.
- I understand that my participation in this study is voluntary and that I am completely free to refuse to participate or to withdraw from this study at any time without changing in any way the quality of care that I receive.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I will receive a signed copy of this consent form for my own records.
- I have read this consent form and I freely consent to participate in this study.

SIGNATURES

_____	_____	_____
Participant's Signature	Printed Name	Date

_____	_____	_____	_____
Signature of Person Obtaining Consent	Printed Name	Study Role	Date

Appendix B: Ethics Certificates

B.1 UBC Clinical Research Ethics Certificate

The University of British Columbia
Office of Research (Services) Ethics
Clinical Research Ethics Board – Room 210, 828 West 10th Avenue, Vancouver, BC V5Z 1L8

ETHICS CERTIFICATE OF FULL BOARD APPROVAL

PRINCIPAL INVESTIGATOR: Neil Eves	INSTITUTION / DEPARTMENT: UBC/UBCO Health & Social Development/UBCO Health and Exercise Sciences	UBC CREB NUMBER: H14-01718																																							
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SPONSORING AGENCIES: UBCO Faculty of Health and Social Development - "The Anti-inflammatory Effects of Exercise in Patients with Chronic Obstructive Pulmonary Disease"																																									
PROJECT TITLE: Mechanisms of Exertional Dyspnea in Postsurgical Patients with Non-Small Cell Lung Cancer																																									
THE CURRENT UBC CREB APPROVAL FOR THIS STUDY EXPIRES: August 12, 2015 The full UBC Clinical Research Ethics Board has reviewed the above described research project, including associated documentation noted below, and finds the research project acceptable on ethical grounds for research involving human subjects and hereby grants approval. This approval applies to research ethics issues only. The approval does not obligate an institution or any of its departments to proceed with activation of the study. The Principal Investigator for the study is responsible for identifying and ensuring that resource impacts from this study on any institution are properly negotiated, and that other institutional policies are followed. The REB assumes that investigators and the coordinating office of all trials continuously review new information for findings that indicate a change should be made to the protocol, consent documents or conduct of the trial and that such changes will be brought to the attention of the REB in a timely manner.																																									
REB FULL BOARD MEETING REVIEW DATE: August 12, 2014																																									
DOCUMENTS INCLUDED IN THIS APPROVAL:		DATE DOCUMENTS APPROVED:																																							
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CERTIFICATION: In respect of clinical trials: 1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations. 2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices. 3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing. The documentation included for the above-named project has been reviewed by the UBC CREB, and the research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved by the UBC CREB.																																									
<p style="text-align: center;">Approval of the Clinical Research Ethics Board by</p> <p style="text-align: center;">Dr. Peter Loewen, Chair</p>																																									

B.2 Interior Health Research Ethics Certificate

Interior Health

Research Ethics Board
220 - 1815 Kirschner Road
Kelowna, B.C., V1Y 4N7

Certificate of Research Ethics Board Delegated Approval

Principal Investigator: Dr. Neil Eves	Institution of Primary Association UBC Okanagan	IH Research File Identifier 2014-15-017-H
Study Title: Mechanisms of Exertional Dyspnea in Postsurgical Patients with Non-Small Cell Lung Cancer		
IH Administrative Contact Greg Cutforth		Co-Investigators Megan Harper, UBCO
Sponsoring/Funding Agencies UBC funding		IH Departments Involved in Research Study Kelowna General Hospital Respiratory Department
Documents Covered by this Approval Research Proposal 2 September 4, 2014 Consent Form 2 September 4, 2014 Ventolin Monograph 1 October 3, 2007 Recruitment Poster 1 July 31, 2014 MDP Questionnaire 1 April 11, 2008 Consent to Contact 2 September 4, 2014 PI Response to Provisos September 4, 2014		Certificate of Approval from Primary REB UBC CREB September 12, 2014 (H14-01718)
Certification It is the assessment of IH that this research study poses minimal risk to human participants and therefore qualifies for delegated review. The above named documents have been reviewed according to Interior Health Research Ethics Board policy and the procedures were found to be acceptable on ethical grounds for research involving human participants. This Certificate of Approval is valid for the term specified below provided there are no changes in the study procedures. <i>The Interior Health Research Ethics Board is in compliance with the ethical principles presented in the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.</i>		
Conditions for Approval It is the responsibility of the Principal Investigator to inform the IH Research Ethics Board if there are changes to consents or other materials used with human participants. Changes must be submitted to the IH Research Ethics Office for review and approval prior to implementation. It is the responsibility of the Principal Investigator to inform the IH Research Ethics Office if human participants experience serious or unexpected events.		
Approval Date 12 September 2014		Approval Term 1 year
IH Authorized Signature Wendy Petillion, Chair, Interior Health Research Ethics Board		
		Date