EFFECT OF ACUTE LUNG VOLUME REDUCTION SURGERY ON LUNG MECHANICS AND MAXIMAL FLOW IN A CANINE MODEL OF UPPER LOBE EMPHYSEMA

BY

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A Thesis/Practicum submitted to the Faculty of Graduate Studies of the University of Manitoba in partial fulfillment of the requirements of the degree of

Master of Science

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ABSTRACT

In severe pulmonary emphysema, lung volume reduction surgery (LVRS) is a palliative surgical procedure that has been shown to improve lung function and maximal expiratory flow in selected patients. However, in the immediate perioperative period, the acute physiologic changes following LVRS are not fully understood and may represent a period of potentially high morbidity. The changes in parameters of maximal expiratory flow limitation that occur immediately following lung volume reduction surgery in a canine model of upper lobe emphysema were investigated in this study.

Healthy dogs were randomized to undergo development of bilateral upper lobe emphysema (n=9) through repeated bronchoscopic instillations of the proteolytic enzyme papain or to serve as healthy controls (n=8). Satisfactory development of emphysema was confirmed by measuring lung volumes at baseline and after serial papain administration and noting an increase in total lung capacity (TLC) to 120% of the pre-emphysema value. Dogs with and without emphysema were then randomized to have LVRS or to serve in time control groups.

All dogs had pulmonary function tests (PFTs) and airway resistance performed while the animal was anesthetized and placed in a volume displacement plethysmograph. Lung volumes were measured using a Krogh spirometer. Maximal expiratory flow (V_{max}) was measured by a pneumotachograph placed between the spirometer and the plethysmograph. Parameters of expiratory flow limitation were also determined while the animal was placed in the plethysmograph following temporary surgical placement of a steel tracheostomy tube. The lungs were inflated to a standard transpulmonary pressure (P_{tp}) of 30 cm H_20, so

that the degree of lung inflation would not affect the results pre- and post-LVRS. A small pressure sensor was placed into the airway (Pitot-Static tube) under bronchoscopic guidance in order to determine airway lateral (P_{lat}) and end-on pressure (P_{end}) as well as the site of flow limitation (termed the choke-point - CP) during forced deflation. In the analysis, V_{max}, CP site, lung elastic recoil pressure (P_{el}), and intrabronchial pressures were measured at 70%, 50%, and 30% vital capacity (VC) at each study interval. The flow limitation studies were performed after emphysema was produced and repeated approximately 1 month later, immediately after acute LVRS was performed in the animals randomized to surgery, or at comparable intervals in the non-LVRS dogs.

Papain emphysema was associated with significant increases in TLC, residual volume (RV), and functional residual capacity (FRC) as compared with pre-emphysema measurements. Post-emphysema, the lung pressure-volume curve was shifted upward and to the left as compared to baseline, indicating that the major physiological effect that occurred after papain administration was air trapping. V_{max} in the emphysema dogs were significantly reduced compared to those found in the non-emphysema dogs at the three lung volumes studied. In the emphysema dogs, CP at the two higher lung volumes were generally found more upstream as compared to the non-emphysema dogs. Cross-sectional area (A*) at the CP were significantly less than corresponding measurements determined in the non-emphysema dogs.

Immediately after LVRS was performed, TLC, VC, and IC in the emphysema dogs (n=6) returned to near pre-emphysema values, while TLC, VC, and IC decreased approximately 20% in the non-emphysema dogs (n=5). Respiratory compliance was reduced following LVRS in both the emphysema and non-emphysema dogs. Pressure-

volume curves obtained after LVRS in both the emphysema and non-emphysema dogs were shifted downward and to the right as compared with the respective pre-surgery curves. Following surgery, P_{el} at the three fractions of VC increased in both the emphysema and non-emphysema dogs. V_{max} in the emphysema dogs decreased at the two higher lung volumes as compared with pre-LVRS, while V_{max} was slightly increased at the lowest lung volume. In both the emphysema and non-emphysema dogs, LVRS was associated with a tendency for P_{fr} and frictional resistance to increase as compared to pre-surgery.

In summary, LVRS in the acute postoperative period is associated with a decrease in respiratory compliance and an increase in P_{el}, while V_{max} did not increase. Postoperatively, these acute effects may lead to difficulty in weaning patients from mechanical ventilation and may contribute to morbidity and mortality. Understanding these complex changes in lung mechanics following LVRS may help to better select patients who would benefit from the surgery.

CHAPTER I. INTRODUCTION

In pulmonary emphysema, severe disease is characterized by shortness of breath on minimal exertion or at rest, as well as limited exercise tolerance.[1] Pathologically, emphysema is defined by airspace dilation with destruction of alveolar walls.[1-4] This process leads to a loss of lung recoil and airway obstruction. Airway obstruction occurs because loss of elasticity in emphysematous lung units results in less outward traction on bronchi and small airways, that in turn narrows the airways as compared with healthy lungs. Pulmonary function tests show marked hyperinflation, airway obstruction, and loss of lung elasticity. The most common type of emphysema is associated with cigarette smoking, and heterogeneity of the emphysematous process is often observed with the predominance of bullae or emphysematous areas located in the upper lobes.[2] In disease caused by α-1 antitrypsin deficiency, the emphysema is usually homogenous with diffuse involvement of all lung units.[2]

Medical therapy for emphysema remains palliative.[3] Although bronchodilator and steroid therapy are usually administered, these treatments are of limited and transient value and the quality of life of patients with emphysema is poor. Over the last few years, there has been intense interest in a surgical procedure for palliative therapy in severe emphysema, termed lung volume reduction surgery (LVRS).[5] Although various operative techniques have been described, in the most common surgical approach a midline sternotomy is performed, after which the most severely diseased emphysematous regions of both lungs are removed. The surgery involves excision of 20% to 30% of the parenchyma of each lung. In a landmark study, Cooper et al[5] performed this operation in a select group

of 20 patients with severe emphysema and found that there was a striking improvement in overall lung function, exercise tolerance, and quality of life.

CHAPTER II. LITERATURE REVIEW

A. HISTORY OF LUNG VOLUME REDUCTION SURGERY

Dr. Otto Brantigan is credited with the first therapeutic surgical procedure which involved resection of diseased lung tissue in the treatment of patients with nonbullous emphysema[6-8]. Brantigan observed that the hyperinflated lungs of patients with severe emphysema were grossly oversized relative to the thoracic cavity, thereby reducing function. Furthermore, Brantigan noted that there were variable degrees of involvement of parenchymal destruction within the emphysematous lung with some areas of severely diseased lung tissue that could no longer contribute to normal gas exchange and with some areas of relatively preserved lung parenchyma. The diseased hyperexpanded lung tissue was essentially compressing the remaining healthy lung and inhibiting its normal expansion within the thoracic cavity. In addition, he noted that lung parenchymal destruction diminished the tethering properties upon small bronchi, thereby reducing peripheral airway cross sectional diameter and limiting flow. Brantigan then hypothesized that resecting or plicating the most severely diseased emphysematous lung would allow re-expansion of the remaining healthy lung units and would optimize parenchymal tethering upon peripheral airways resulting in increased bronchiolar air flow. Following careful evaluation and investigation of selected patients with emphysema, 56 had lung volume reduction surgery via unilateral thoracotomy, while 14 had staged bilateral lung reduction[6-8]. The procedure involved resection of 20-30% of the most severely diseased lung along with lung denervation using radical hilar stripping. Despite noting symptomatic improvement in 75% of the patients, postoperative mortality was high (16%). Early

attempts to duplicate Brantigan's procedure resulted in unacceptably high morbidity and mortality rates.[9] LVRS was deemed too risky for therapeutic use in emphysema patients and largely abandoned.

Dr. Joel Cooper and colleagues at Washington University in St. Louis, Missouri resurrected the work of Brantigan in the mid-1990s during their observations following single lung transplantation for patients with severe emphysema.[5] Although pulmonary function of patients following single lung transplantation did not improve to the same degree as patients who had undergone bilateral transplantation, Cooper noted that single lung transplant recipients had better than expected symptomatic improvement. He also observed that the previously hyperexpanded chest wall had assumed a more normal configuration on both the transplanted and nontransplanted hemithoraces following single lung transplantation. Cooper reasoned that the "volume reduction" that occurred following single lung transplantation and subsequent anatomic reconfiguration allowed improved elastic recoil and better diaphragmatic and intercostal muscle function for both the transplanted and native lung. Cooper then considered which patients with end-stage emphysema would benefit from lung volume reduction. After careful evaluation and preoperative pulmonary rehabilitation of selected emphysema patients, Cooper and colleagues performed bilateral lung volume reduction via median sternotomy. Approximately 30% of each lung volume was resected using a linear stapler, targeting the most severely diseased lung units, while the staple lines were buttressed with bovine pericardium in order to minimize post operative air leak. Cooper reported the outcomes of the first 20 patients who had undergone LVRS. These patients demonstrated marked improvement in lung function with 82% increase in mean forced expiratory volume in one

second (FEV_1), as well as significant symptomatic improvement in terms of dyspnea, exercise tolerance and quality of life.[5] More importantly, no patients died in the post operative period. Following Cooper's outstanding results, numerous other surgeons around the world began performing lung volume reduction surgery in their own institutions. The relatively new surgical procedure received the attention of U.S. Medicare and the Health Care Financing Administration (HCFA) when the number of Medicare claims for lung volume reduction surgery grew from approximately 200 in 1993 to 2000 in 1995.[10] In contrast to the results reported by Cooper et al, however, some centres reported high postoperative mortality rates following surgery, and these studies prompted more conclusive data about the utility of LVRS in emphysema.

The controversy surrounding LVRS prompted the creation of a large scale, multi-center randomized trial comparing surgery and medical therapy for patients with severe emphysema. The National Emphysema Treatment Trial (NETT) was carried out in 18 selected U.S. centers and supported by the HCFA, the National Institute of Health, the Agency for Healthcare Policy and Research and the National Heart, Blood and Lung Institute.[11] An interim analysis during the trial identified a subgroup of patients as being at high risk for death from surgery.[12] The high risk subgroup had FEV1 < 20% of their predicted value and either a homogeneous distribution of emphysema or a carbon monoxide diffusing capacity < 20%. The 30-day mortality following surgery was 16% versus 0% in the medical group and subsequently these patients were deemed ineligible for randomization into the trial. Analysis of the final results showed no differences in overall mortality between the medical and surgical groups.[11] There was however a significant survival advantage in the surgery group among a subgroup of patients with predominantly

upper lobe emphysema and low preoperative exercise capacity. The patients in this surgery group were also found to have a significantly higher improvement in exercise capacity at 24 months compared with the medical group. In addition, other subgroups of patients, defined by the presence or absence of upper lobe predominant emphysema and low or high preoperative exercise capacity, were found to have significant improvements following surgery compared with their respective medical groups. Patients with predominantly upper lobe disease and high exercise capacity in the surgery group had higher improvements in exercise capacity and health related quality of life scores. Patients with non-upper lobe disease and low exercise capacity randomized to surgery also had higher improvements in quality of life scores. Only the subgroup of patients with both non-upper lobe predominance and high baseline exercise capacity demonstrated no improvements following LVRS and furthermore were at higher risk of death following surgery. Following the conclusion of the NETT and in light of the results of the trial, Medicare resumed coverage for LVRS for patients meeting the criteria of severe upper lobe predominant or severe non upper lobe emphysema with low exercise capacity and lacking the factors of the high risk group identified in the NETT interim analysis.[13]

B. METHODS OF LUNG VOLUME REDUCTION SURGERY

Although the fundamental principles of LVRS have been present for almost 50 years, the technical challenges encountered by Brantigan continue to challenge thoracic surgeons today.

Brantigan's first description of LVRS was that of a simple clamp and suture technique where the obviously diseased lung tissue was excised and the walls of the remaining space

approximated with interrupted sutures of chromic catgut.[6] Brantigan recognized the potential hazards of resecting emphysematous tissue and cautioned against removing excessive volume that would result in suboptimal lung expansion and formation of air leaks. Indeed, he described meticulous searching for and suture repair of air leaks following resection. In addition to the volume reduction technique, Brantigan added a denervation procedure consisting of lysis of vagal branches to the lung, heart and mediastinum as well as a periarterial, perivenous and peribronchial sympathectomy.[6] The rationale for the denervation procedure was to reduce bronchial secretions, decrease pulmonary artery pressure and relieve bronchospasm. Although symptomatic improvement was noted in the majority of patients, operative mortality was high in Brantigan's original series (18%).[7] Attempts to duplicate Brantigan's surgery at other centers met with limited success and higher mortality.[9] The procedure was abandoned until Cooper and colleagues resurrected Brantigan's original concept[5] (see *History of Lung Volume Reduction Surgery*). In terms of the technique of LVRS, Cooper performed the surgery via median sternotomy rather than thoracotomy as used by Brantigan. Also unique to Cooper's modification was the use of surgical staples buttressed with bovine pericardium to help decrease the incidence of post operative air leaks. Cooper also performed a bilateral lung reduction rather than a unilateral procedure. A more recent study has shown that bilateral LVRS is superior to unilateral procedures in terms of functional improvement.[14] While this study showed no difference in overall morbidity or mortality, other authors report higher operative mortality with the bilateral approach.[15,16]

As the typical patient undergoing LVRS is elderly with limited functional reserve, surgeons have looked to minimally invasive means of performing the reduction procedure.

The use of open vs. thoracoscopic approach for LVRS remains controversial. A retrospective review by Kotloff et al. comparing median sternotomy approach and VATS (video assisted thoracic surgery) approach demonstrated a significantly higher in-hospital mortality with the open technique.[17] However, other studies did not show a difference in mortality or functional outcome between open and VATS LVRS.[18,19] More recently, a multi-center review of patients enrolled in the National Emphysema Treatment Trial (NETT) compared 359 patients who underwent LVRS via sternotomy with 152 patients who received LVRS via VATS.[20] There were no differences in mortality or complications. However, median hospital stay and associated costs were increased in the sternotomy group. In the absence of randomized prospective trials, the optimal approach to LVRS should be largely determined by individual surgeon preference and center experience. Each approach appears to have distinct advantages. While the sternotomy approach would allow complete control of the surgical field, use of the thoracoscope offers superior visualization in less accessible areas of the thorax. The use of grasping instruments necessary in VATS may lead to potential tears and subsequent air leaks that are potentially minimized through an open technique that utilizes minimal tissue handling of delicate parenchyma.[21] While LVRS preformed by VATS results in less extensive incisions and theoretically less post-operative pain, surgical treatment for emphysema should be individualized to the patient and within the local expertise of the treating surgeon.

The technique of parenchymal resection in LVRS has been approached with a number of modalities to minimize the potential post surgical morbidity that is common with this patient population. While the use of buttressed staplers has been widely used in the majority of centers, their effectiveness of this procedure in decreasing the incidence of air

leak has been questioned. Both porcine pericardium[22] and synthetic polytetrafluorethylene material[23] have been used in clinical practice. However, a randomized trial of pericardial buttressed stapler device compared to no buttressing for LVRS showed no significant differences in the duration of air leak.[24] The use of laser ablation to resect emphysematous lung tissue has been utilized. Wakabayashi reported a series of 443 patients who underwent thoracoscopic laser pneumoplasty for diffuse bullous emphysema and described symptomatic improvement in 87% of patients.[25] However, a randomized prospective trial comparing unilateral stapled thoracoscopic LVRS versus laser bullectomy by McKenna and colleagues[26] demonstrated a significantly higher improvement in post-operative FEV_1 at 6 months as well as a higher rate of discontinuation of supplemental oxygen in the stapled group. Also, a significantly higher incidence of delayed pneumothorax was found in the laser group. Subsequently, laser ablation has generally fallen out of favor as a means of performing LVRS.[14,20,27,28]

A novel means of lung volume reduction has been reported using a vacuum assisted lung tissue capture and reinforcement system (VALR Surgical System; Spiration Inc.; Redmond, Washington, see also **Figure 1** at end of *Materials and Methods* Section).[29,30] The device consists of a silicone compression sleeve loaded into a cylindrical introducer attached to a regulated vacuum control device. The compression sleeve has a compression band fitted with lugs at the proximal end within its inner circumference to facilitate secure placement once deployed. When the vacuum is activated, targeted lung tissue is atraumatically suctioned up into the compression sleeve. Once the desired amount of tissue has been delivered into the sleeve, the sleeve is released from the introducer by forward advancement of the outer cylinder of the introducer. Once deployed, the silicone sleeve

acts to radially compress the captured lung tissue. At the proximal end, the compression band and lugs act to secure placement upon the lung parenchyma. The proximal end is further secured in place by placement of 2 perpendicularly oriented sutures through the compression sleeve just above the lugs within the compression band. Following suture placement, the remainder of the sleeve with its captured lung tissue is resected, leaving behind the compression band on the lung parenchyma. Studies of animal models have shown the effectiveness of the VALR system in producing safe volume reduction and in eliminating post-operative air leaks.[29,30] Since the current investigators have had previous experience with the use of the VALR device in previous experiments in LVRS,[29] it was the chosen method for performing the volume reduction in the present study.

Regardless of the surgical technique used to perform LVRS, questions remain with regards to the heterogeneity of response following volume reduction and determining the exact physiologic mechanisms whereby lung function is improved following surgery.

C. PHYSIOLOGIC MECHANISMS OF IMPROVEMENT FOLLOWING LUNG VOLUME REDUCTION SURGERY

Brantigan's original hypothesis that removal of diseased hyperinflated lung units would improve symptoms by improving lung elastic recoil and increasing peripheral airway tethering and thus airway diameter[7] has been validated in several experimental studies. An increase in elastic recoil has been observed following LVRS by numerous investigators, but the exact mechanisms by which higher recoil pressures occur have not yet been fully elucidated. Sciurba and colleagues[31] studied 20 patients with diffuse emphysema prior to