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

and 3 months following LVRS and found a significant increase in maximal elastic recoil pressure as well as significantly higher FEV_1 and forced vital capacity (FVC). Similarly, Gelb and colleagues[32] found higher elastic recoil pressures as well as increased airway conductance, FEV_1 and FVC following LVRS compared with preoperative values in 12 patients. In addition, analysis of expiratory flow-lung recoil pressure curves showed improved airway conductance, suggesting improvement in airway luminal diameter as a result of higher lung recoil pressures and thus improved flow parameters. While there is consistency of response to LVRS in these studies in terms of resultant increased flow and elastic recoil, it should be noted that differences in inspiratory transpulmonary pressure and muscle strength before and after surgery must also be considered. In particular, the capacity of the a patient to generate a sufficiently high transpulmonary pressure during a full voluntary inspiration following LVRS may be increased compared to before surgery because the removal of hyperinflated lung units may allow diaphragm muscle fibers to contract more efficiently. This results in an enhanced ability to generate a higher inspiratory transpulmonary pressure post LVRS. Specifically, the adverse effects of hyperinflation on diaphragm function, including precontractile length foreshortening,[33,34] reduced radius of curvature,[33] increased elastic load,[34] impaired diaphragm blood flow[35] and reduced area of apposition of the costal diaphragm and chest wall[36,37] have been attenuated. Brantigan first observed the corresponding change in contour of the diaphragm when comparing chest roentgenograms that evolved from a flattened shape preoperatively to a more normal upward convexity following volume reduction.[7] The same radiographic changes in diaphragm configuration were reaffirmed by Cooper.[5] Looking specifically at diaphragm function, Criner and colleagues[38] studied the effects of LVRS on diaphragm

strength using maximum static inspiratory effort, sniff tests and percutaneous phrenic nerve stimulation with improvements in all parameters following LVRS compared to control patients undergoing pulmonary rehabilitation. Laghi and colleagues found an increase in diaphragmatic pressure generation and neuromechanical coupling following LVRS which correlated to improvements in 6-minute walk distance and reduction of dyspnea.[39] Other changes in respiratory muscle function following LVRS include increases in diaphragm length,[40] surface area and rib cage zone of apposition,[41] reduction of diaphragm neural drive[42] and alterations in diaphragm muscle gene expression.[43]

While it is generally believed that a relative increase in lung elastic recoil pressure following LVRS leads to an increase in the driving force during forced expiration, the specific changes in airway conductance and the mechanism of increase in maximal flows following surgery are unclear. A number of studies have investigated the effects of LVRS within the context of expiratory flow limitation. Theories pertinent to maximal flow are described below.

D. THEORIES OF MAXIMAL EXPIRATORY FLOW LIMITATION

Fry first described the concept of expiratory flow limitation.[44] He noted that, during an expiratory flow maneuver, as one progressively increased pleural pressure by increasing muscular effort, flow increased until a maximum value was reached. Any additional increases in muscular effort once a critical effort had been achieved failed to increase flow any further. In his complex analysis using a collapsible rubber tube hydraulic model, Fry calculated maximum flow-pressure curves as a function of several system constants including transmural pressure change, tube compliance, length, radius as well as water

density.[44] However, his single bronchial segment model was limited when trying to accurately describe specific events occurring along the entire compressed segment.

Pride and colleagues[45] described the dynamics of flow using the concept of the "Starling Resistor." They considered the interrelationship between outlet pressure (P_{ao}), the pressure at the end of the tube equal to atmospheric pressure; pleural pressure (P_{pl}) around the tube; and alveolar pressure (P_{al}). Maximal expiratory flow (V_{max}) is determined by the difference in pressure between Pal and the critical transmural pressure (P_{tm}') of maximal wall stability, above which the airway lumen collapses and limits flow. Mead and associates[46] explained V_{max} using the "equal pressure point" (EPP) model. EPP is defined as the location within the airway where lateral airway pressure = P_{pl} and therefore where transmural pressure = 0. The difference between P_{al} and P_{pl} is recoil pressure (P_{el}) and is the driving pressure for flow. Upstream from the EPP, $P_{al} > P_{pl}$ and P_{tm}' is positive, while downstream from EPP, P_{tm}' is negative. During expiration, there is a pressure loss from alveoli along the airway. As P_{pl} increases with more respiratory effort, EPP move upstream from trachea to alveoli. EPP become fixed when downstream from EPP the resistance of the compressed segment reaches the threshold to limit flow, and thus maximal flow has been reached. Mathematically, V_{max} is determined by lung elastic recoil (P_{el}) and upstream airway resistance (R_{us}) such that: $V_{max} = P_{el} / R_{us}$

Dawson and Elliott's "wave-speed theory" of maximal flow limitation[47,48] appears to be the most rigorous in explaining the mechanism of flow limitation in normal and diseased lungs. According to this model, flow becomes limited when at a site within the airway, termed the choke point (CP), tube-wave speed is reached. At the CP, gas velocity is equal to the speed of propagation of pressure pulse waves along the airway wall, and maximal

velocity has been reached. Each point along the airway has a critical value tube-wave speed, and therefore each bronchial cross-section can develop a CP. The critical value is dependent upon the physical characteristics of the tube and the density of air. At any given lung volume, the factors determining CP location and cross-sectional area are P_{el}, airway compliance and frictional pressure losses along the airway. V_{max} is equal to $(A^3/\rho qK)^{1/2}$, where A, ρ, q and K are airway cross-sectional area at CP, gas density, correction factor for departure from blunt velocity profile and compliance at CP, respectively. The CP occurs where gas velocity first reaches the local wave speed. Upstream from the CP, the airway segment remains fixed at constant geometry. However, downstream from the CP, energy is dissipated in the form of a large pressure drop since flow is unable to increase and downstream airway geometry may vary. The wave-speed theory of flow limitation has been tested extensively[48-56] and appears to best explain the mechanisms of flow limitation in a variety of disease conditions. Therefore the present study is interpreted using the concepts of the wave-speed model.

E. PREVIOUS STUDIES OF MAXIMAL FLOW IN LUNG VOLUME REDUCTION SURGERY

Gelb and associates[32] studied the effects of LVRS limitation using the Starling resistor or equal pressure point models of flow limitation.[45,46] Gelb constructed maximal flow-elastic recoil pressure curves to determine airway conductance (G_s) of the S segment (ie. the portion of airway extending from alveoli up to and including the flow limiting segment) before and after LVRS and found significantly higher conductance following surgery. In addition, following LVRS a significant decrease in the critical transmural pressures (P_{tm}') in the flow limiting segment was observed as well as higher elastic recoil pressure

postoperatively. They concluded that the improved elastic recoil of the lung after surgery enhances airway radial traction, increasing patency and improving expiratory flow. However, other studies of LVRS using the same models of flow limitation have demonstrated conflicting results. Scharf and colleagues[57] studied 9 patients with severe emphysema and found no significant changes in Gs or airway closing pressure following LVRS, even though there was a significant increase in P_{el} after surgery. There was a rather heterogeneous response of parameters of flow limitation following LVRS despite significantly higher FEV_1, FVC and P_{el}. This led the authors to suspect that an increase in P_{el} was the predominant factor responsible for improvement in expiratory flows. Similarly, Ingenito and associates[58] did not observe any significant difference in P_{tm}' or small airway conductance when they examined preoperative and postoperative parameters of expiratory flow in 37 patients undergoing LVRS, although FEV_1, V_{max} and P_{el} all increased significantly for the group as a whole following LVRS. Ingenito also noted that, among the cohort of patients that were "responders" (defined as those patients who had an increase in $FEV_1 \geq 12\%$), improvements in V_{max} and FEV_1 correlated significantly with changes in recoil pressure "weighted" by preoperative airflow conductance. The patients who responded best to LVRS had lower preoperative recoil pressures but higher preoperative airway conductance. Patients with intrinsic airway disease from chronic inflammation may have reduced wall compliance and thus be more resistant to outward distending forces resulting from an increased P_{el} following LVRS.[28,59] Thus, the fact that patients who responded favorably to LVRS did not exhibit any significant changes in airway conductance or P_{tm}' suggests that enhanced airway radial traction following surgery may not be the main mechanism of increased expiratory flow.[58]

While there have been important insights into the changes in parameters of expiratory flow limitation following LVRS, the majority of studies have examined patients within the equal pressure point or Starling resistor model.[57,58] There have been no studies to date that have interpreted flow parameter changes following LVRS within the framework of wave speed theory,[47,48] which the author feels to be the optimal model for the study of flow limitation in disease states. While previous studies have indirectly measured changes in airway properties of flow limitation, utilizing the concepts of wave speed theory, more precise measurements of choke point location, pressure and cross-sectional area are possible and would add new insight into further understanding the physiologic alterations that occur following LVRS.

The majority of studies of LVRS to date have examined physiologic changes several weeks to months following surgery.[5,11,31,32,57,58] Little work has been presented on the physiologic changes that occur immediately following LVRS, yet this postoperative recovery period represents a time of high morbidity and mortality for certain subgroups of emphysema patients with limited physiologic reserves.[12] Therefore, the alteration in respiratory mechanics occurring during the immediate postoperative time is important in order to optimize the acute recovery period. Barnas and colleagues[60] studied changes in lung and chest wall mechanics immediately before and after LVRS in 9 consecutive anesthetized patients. Immediately following surgery, Barnas noted significant elevations in lung elastance and resistance during the inspiratory phase, suggesting higher work of breathing for LVRS patients in the acute postoperative period.

While numerous studies have investigated the complex physiologic changes following LVRS, much remains unknown about the exact mechanisms of altered lung

mechanics following surgery. It is obvious that further insight is imperative in order to choose which patients may best benefit from LVRS.

F. EXPERIMENTAL MODELS OF EMPHYSEMA AND LUNG VOLUME REDUCTION SURGERY

As much of the physiologic alterations following LVRS are unknown, animal models of emphysema are needed for further study of the effects of surgery on lung mechanics and function.

Papain, a proteolytic enzyme that degrades the amorphous elastin component of elastic fibres,[61] was first used by Gross and colleagues who observed changes in rat lungs that resembled human emphysema.[62] The current laboratory has previously developed a canine model of emphysema using a technique of repeated intrabronchial instillations of papain under bronchoscopic visualization into the targeted areas a few weeks apart until the desired changes in lung volume and mechanics have occurred.[29,54,56,63,64] Other techniques for producing emphysema in various animal models have been used. Several investigators have used aerosolized porcine elastase administered via endotracheal tube in rabbits to produce diffuse emphysema.[65,66] Brenner and colleagues[67] used intratracheal carrageenan and intravenous Sephadex beads to produce bullous emphysema in rabbits. The present model of intrabronchial instillation of papain offers the advantage of producing heterogenous emphysema predominantly in the upper lobes with relative sparing of the remaining lungs. This pattern of emphysema is recognized to be the most responsive to LVRS in terms of improvement in both measured lung function and symptoms.[11] The histologic changes induced by papain are characteristic of panacinar emphysema, similar to

that found in α-1 antitrypsin deficiency.[68] The mechanical properties of papain-induced emphysema, namely reduced elastic recoil and increased compliance, have been noted in past studies in which diffuse emphysema has been produced.[63,64,69] Increased lung volumes that include total lung capacity (TLC), vital capacity (VC), functional residual capacity (FRC) and residual volume (RV) have been consistently produced following development of papain-induced emphysema. Because the present experiment uses an upper lobe model of emphysema, the changes from baseline are not as dramatic as a diffuse emphysema model. However, the associated changes in lung mechanics in the emphysematous lungs would still be apparent. Therefore, the present study using a canine model of papain-induced upper lobe emphysema is ideal for examining the changes in lung mechanics and maximal flow parameters following LVRS.

CHAPTER III. MATERIALS AND METHODS

A. ANIMAL SUBJECTS

This study was approved by the University of Manitoba Central Animal Care Committee and all animals involved in the study were treated in accordance with the "Guide for the Care and Use of Laboratory Animals" published by the US National Institute of Health (NIH Publication No 85-23, revised 1996). A total of 17 dogs were used in the study. The animals weighed between 19 – 26 kg. All animals were immunized and examined by a veterinarian and were determined not to have any acute illnesses.

A.i. EXPERIMENTAL GROUPS

The study consisted of 4 groups, two emphysema groups and two non-emphysema groups. Nine dogs were included in the two emphysema groups. Six of the nine dogs underwent LVRS, while 3 dogs were included as an emphysema time control group. In the two non-emphysema groups, of the eight dogs studied, 5 dogs underwent LVRS, while 3 dogs were included in the non-emphysema time control group.

A.ii. DEVELOPMENT OF CANINE EMPHYSEMA MODEL

In the nine dogs randomized to the emphysema groups, the lesion was induced as previously described[56,63,70] A solution of the proteolytic enzyme papain (57.5-69.0 mg, Sigma Chemical Co., St. Louis, MO) mixed with 18 ml of normal saline was used for the intrabronchial instillations. During the procedure, the animal was anesthetized with

intravenous pentobarbital (Somnotol® MTC Pharmaceuticals, 30 mg/kg) and placed on mechanical ventilation. A flexible bronchoscope was passed through the endotracheal tube and used to locate the targeted upper lobe bronchus. A catheter was guided into one of the upper lobe segments and the papain solution was instilled under direct visualization. Once completed, the bronchoscope was withdrawn and the animal was placed in reverse Trendelenberg position with the instilled side down to prevent spillage of the papain solution out of the upper lobe airways. The dogs were ventilated for approximately 6 hours until breathing spontaneously and were brought back to animal housing for recovery. Intravenous antibiotics were given (clindamycin 5 mg/kg and gentamycin 7 mg/kg) prior to papain instillation and 24 hours post-instillation for infection prophylaxis. The process was repeated approximately 7 to 10 days later in the contralateral upper lobe. By means of infusion of the papain mixture into different upper lobe segmental bronchi on different occasions (approximately 8 instillations into each upper lobe over a 4 month interval), it was possible to produce relatively uniform upper lobe emphysema in each lung. In the control groups, it was previously shown that repeated instillations of saline solution had no effect of pulmonary function over a similar duration of treatment, so that this procedure was not performed in the present protocol.

Satisfactory emphysema development was verified by measuring lung volumes (see *Pulmonary Function Tests*; see **Figure 2**) following completion of serial papain instillations and noting an increase in total lung capacity (TLC) compared to pre-emphysema measurements that were performed prior to the instillations.

B: PULMONARY FUNCTION TESTS

Pulmonary function tests (PFTs) were performed by methods previously described.[71,72] Following induction of anesthesia with intravenous pentobarbital, the animal was intubated with a large balloon cuffed endotracheal tube that did not limit flow. The animal was mechanically ventilated (20 ml/Kg) and then placed in a volume displacement plethysmograph in the left lateral decubitus position. An esophageal balloon was inserted with the tip approximately 5 cm from the gastroesophageal junction to measure pleural surface pressure (P_{pl}). The esophageal balloon was inflated with 0.2 ml of air. Lung volumes were measured using a Krogh spirometer mounted on the plethysmograph. Flow was measured with a pneumotachygraph (Fleisch no. 4) placed between the spirometer and the plethysmograph (see Figure 2).

Airway opening pressure (P_{ao}) was measured from a lateral pressure tap in the endotracheal tube. The airway pressure tap and esophageal balloon catheters were both connected by means of polyethylene catheters to a differential pressure transducer (MP-45, *Validyne*, Northridge, CA). The distal ends of the catheters were connected via 3-way stopcocks to the transducer. By opening or closing the airway or esophageal stopcocks, the output of the pressure transducer could be displayed as P_{ao}, P_{pl}, or transpulmonary pressure ($P_{tp} = P_{ao} - P_{pl}$). Signals for volume, flow and pressure were displayed on a dual beam oscilloscope (*Tektronix Inc.*, Beaverton, OR) and an eight channel A*stro Med, Inc* recorder.

The FRC measurements were obtained by means of the Dubois method[73] in which the animal breathes against a valve that was placed at the airway opening and that was closed at end-expiration. The change in thoracic gas volume (ΔV) as the animal attempts to breathe against the closed airway was plotted against the change in airway opening

pressure (ΔP_{ao}). FRC is equal to $(\Delta V/\Delta P)P$ where P = (atmospheric pressure – water vapor pressure). Following the FRC measurements, expiratory reserve volume (ERV) was obtained by means of withdrawing gas volume from the lungs to P_{tp} = -10 cm H_20 in which a 1 litre volume syringe was attached to the airway opening. The lungs were then inflated to TLC (defined as Ptp = 30 cm H_20) by means of a positive pressure air source attached to the airway opening. Inspiratory capacity (IC) was calculated by: IC = TLC – FRC. RV was calculated by: RV = FRC – ERV. Quasi-static deflation P_{tp} vs. volume curves from TLC to RV were recorded; the animal's lungs were inflated to P_{tp} = 30 cm H_20, slowly deflated to FRC, then further deflated to RV by means of the 1 litre (L) syringe. The P-V curves were photographed. FRC and other lung volume measurements were repeated following a standard volume history to P_{tp} = 30 cm H_20.

After a standard volume history, measurements of compliances of the lung (C_L), chest wall (C_{cw}) and pulmonary system (C_{ps}) were calculated by dividing the change in volume by the change in pressure ($C=\Delta V/\Delta P$) during one complete inspiration-expiration tidal volume cycle on the ventilator.

Airway resistance (R_L) at FRC was calculated following a standard TLC volume history. The forced oscillation technique of Mead and Whittenberger[74] was used in which the lungs were oscillated at a frequency of 4 Hertz (Hz) at 1 litre / second (L/s). R_L was calculated by dividing the change in P_{tp} in phase with flow by flow ($R_L = \Delta P_{tp}$/flow). R_L measurements were obtained with the animal placed in the left lateral decubitus position.

In the emphysema groups, PFT measurements were performed before and after emphysema was produced to ensure an increase in TLC of about 20%. This interval averaged 4 months. Since previous studies showed no change in PFTs in non-emphysema

dogs over this interval, only one set of PFTs was performed in the two nonemphysema control groups.

C. MEASUREMENTS OF EXPIRATORY FLOW LIMITATION

One to two weeks after completion of the PFT measurements in the emphysema and control groups, the animals were anesthetized and mechanically ventilated as previously described. A tracheotomy was performed in which the animal was placed in the supine position. The neck was shaved and cleaned with an antiseptic iodine solution. A small longitudinal neck incision was made and the trachea exposed. A tracheal incision was made and a large bore steel tracheostomy tube placed in the airway and secured with circumferential suture ties to ensure an adequate seal. The distal end of the tracheostomy tube was approximately 25 cm from the carina. For the expiratory flow tests the animal was placed in the plethysmograph in prone position to ensure maximum lung emptying and accurate P_{pl} measurements.[75]

A Pitot-Static tube was used to locate CPs and measure airway pressures. The tube was constructed as previously described[55,75] with two ports at the end of the tube that measure lateral (P_{lat}) and end-on (P_{end}) pressures, respectively (see **Figure 2** at the end of *Materials and Methods*). Each port of the Pitot-Static tube was connected to one port of a separate differential pressure transducer by polyethylene tubing (1.6 mm diameter, 65 cm length). P_{lat} and P_{end} were referenced relative to P_{pl} by placement of another polyethylene catheter within the body box plethysmograph that was attached to the esophageal balloon inserted as previously described. The esophageal balloon catheter was attached to the other port of the two differential pressure transducers by a three-way stopcock, so that airway pressures

could be displayed as P_{lat}-P_{pl} or P_{end}-P_{pl}. When results of Plat and Pend are described in the present study, they are given as transmural pressures (ie. P_{lat}-P_{pl} and P_{end}-P_{pl}.) in which Ppl has been subtracted.

The Pitot-Static tube was placed into the airway through a port in the steel tracheal tube. A flexible bronchoscope was also introduced into the airway through the port. Under bronchoscopic visualization, the tip of the Pitot-Static tube was initially placed into the trachea. The Pitot-Static tube was then advanced down the right mainstem bronchus beyond the right upper lobe bronchus, into the bronchus intermedius, and into the right lower lobe bronchi to identify CP at the different lung volumes as previously described.[55,75] The Pitot-Static tube was maintained in its axial orientation by bronchoscopic visualization. The standard locations where the Pitot-Static tube was placed at the different lung volumes to identify CP are further delineated in *Results*.

Forced expiration was conducted in the same manner as previously: the lungs were inflated to TLC (Ptp=30 cm H_20) and the airway was opened to a negative pressure reservoir to allow maximal exhalation (**see Figure 2**). Forced expiratory lung volume as well as corresponding flow-volume curves were recorded on the oscilloscope. The graphical images were photographed and values for flow, pressure and volume measured from the respective curves. Quasi-static pressure-volume curves (P_{el}-V_L) were produced by inflating the lungs to TLC of 30 cm H_20 and slowly deflating to RV such that the flow rate was maintained at <100 ml/sec. P_{el} can be calculated from (Pao-Ppl) during conditions of very low flow rate. Two P_{el} vs. V_L curves were obtained and the graphical images photographed and the values averaged.

The CP was located using pressure criteria previously described:[54,55,63] at a given lung volume, the lateral port of the Pitot-Static tube was positioned at a point within the airway where P_{lat} does not vary with negative pressure applied to the airway opening. However, at a point slightly downstream (< 1 cm), P_{lat} decreased abruptly and varied with negative pressure applied to the airways. Parameters of maximal expiratory flow (P_{lat}, P_{end}, V_L, V_{max}) were measured at 3 lung volumes: 70% vital capacity (VC_{70}), 50% vital capacity (VC_{50}) and 30% vital capacity (VC_{30}) of the VC during each of the measurement studies. Frictional pressure losses (P_{fr}) and airway resistance (R) to CP as well as bronchial cross-sectional area (A*) could be calculated from these values (see *Measured and Calculated Parameters*).

In addition, from the volume vs. time curves, measurements of forced expiration volume (FEV) were determined at 0.25 s ($FEV_{0.25}$), 0.5 s ($FEV_{0.5}$), 0.75 s ($FEV_{0.75}$), and 1.0 s ($FEV_{1.0}$) after initiation of expiration. The percent VC expired at 0.25 s ($FEV_{0.25}$/FVC), 0.5 s ($FEV_{0.5}$/FVC), 0.75 s ($FEV_{0.75}$/FVC) and at 1.0 sec ($FEV_{1.0}$/FVC) were also calculated.

Following completion of maximal expiratory flow tests, the animal was removed from the plethysmograph and the steel tracheal tube removed. The tracheostomy incision was closed and the animal brought back to the recovery kennel. Intramuscular antibiotic injections (clindamycin 5 mg/kg and gentamycin 7 mg/kg) were given for 2 days following the surgery.

D. LUNG VOLUME REDUCTION SURGERY

Measurements of maximal flow were repeated approximately one to two months later, immediately after LVRS was performed or at a comparable interval in the non-LVRS groups. Bilateral upper lobe LVRS was performed in which the animal was anesthetized and intubated in the usual manner. The neck and chest were shaved and an iodine solution applied. Under sterile conditions a median sternotomy was performed using a surgical saw. The upper lobes were identified. The VALR™ apparatus was used to capture the targeted lung tissue within the upper lobe (see *Methods of Lung Volume Reduction Surgery;* see **Figure 1**). For the emphysema subjects, an attempt was made to capture the most diseased portions of the upper lobes. In the control animals, approximately 75% of each upper lobe volume was resected. Following completion of lung volume reduction, the resection sites were checked for air leak by application of saline at the sites of the volume reduction and by observation whether air bubbles were identified. A chest tube was placed in the mediastinum close to the upper lobes and the sternum and chest wall closed with heavy absorbable sutures. The chest tube was connected to -20 cm H_20. The animal was intermittently turned (from supine to left and right lateral decubitus to prone positions) to ensure complete evacuation of residual pleural fluid and air. The chest tube was removed when there was no ongoing efflux of fluid and no air leak. The chest tube site was closed with a pursestring suture.

After completion of LVRS, the steel tracheostomy tube was again inserted into the trachea as previously described. The animal was mechanically ventilated through the tracheal tube and moved into the plethysmograph for post-LVRS PFT and maximal flow measurements that were performed as previously delineated. In the non-LVRS groups, repeat measurements of PFT and maximal flow were obtained at comparable intervals.

Following completion of the experiments, the subject was sacrificed with lethal dose of pentobarbital and intracardiac injection of potassium chloride.

E. MEASURED AND CALCULATED PARAMETERS

The results were analyzed at 70%, 50%, and 30% VC found at each condition. In terms of the Pitot-Static tube measurements, at a given lung volume, the difference between P_{lat} and P_{end} is related to the kinetic energy of gas passing through cross-sectional area (A) and is termed convective acceleration (P_{ca}).[47,48] At a given lung volume, Pc_a can be calculated by the Bernouille equation:[76]

$$P_{ca} = \frac{1}{2} \rho (V_{max})^2 / (A^*)^2$$

where ρ is the gas density (1.12×10^{-3} gm/cm^3). In the non-emphysema groups, lobar emptying was considered to be homogenous. In the control groups, A* could be calculated from the Bernouille equation whether CP were identified in central or more upstream airways, since the flow subtended by the Pitot-Static tube in upstream airways could be assumed to be uniform among comparably sized airways. However, when upper lobe emphysema was produced in the emphysema groups, there would be non-uniform emptying among the lobes, and thus the flow subtended by the Pitot-Static was not representative of that emanating from the other lobes. On the other hand, A* could be calculated in the emphysematous groups when the CP was identified in central airways, since V_{max} represented total flow. In the emphysema group, after LVRS was performed, since the emphysematous units were removed, homogeneous expiration was again assumed and A* was calculated whether the CP was identified in central or more upstream airways.

At a lung volume, frictional pressure losses (P_{fr}) that occurred from alveoli to CP were calculated by:

$$P_{fr} = P_{el} - P_{end}$$

where P_{el} is the average elastic recoil pressure at the respective lung volumes obtained from the quasi-static P_{el}-V_L curves and P_{end} the total pressure at CP.

The airway resistance (R) at the CP for a given V_L was calculated by:

$$R = P_{fr} / V_{max}$$

F. STATISTICS

Statistical analyses included a three way (between-within-within) analysis of variance, a two way (between-within) analysis of variance, a two way (within-within analysis) and paired t-test. A Student Newman Keul's multiple comparison test was used when multiple comparisons were obtained. Results were reported as mean (± 1 SD).

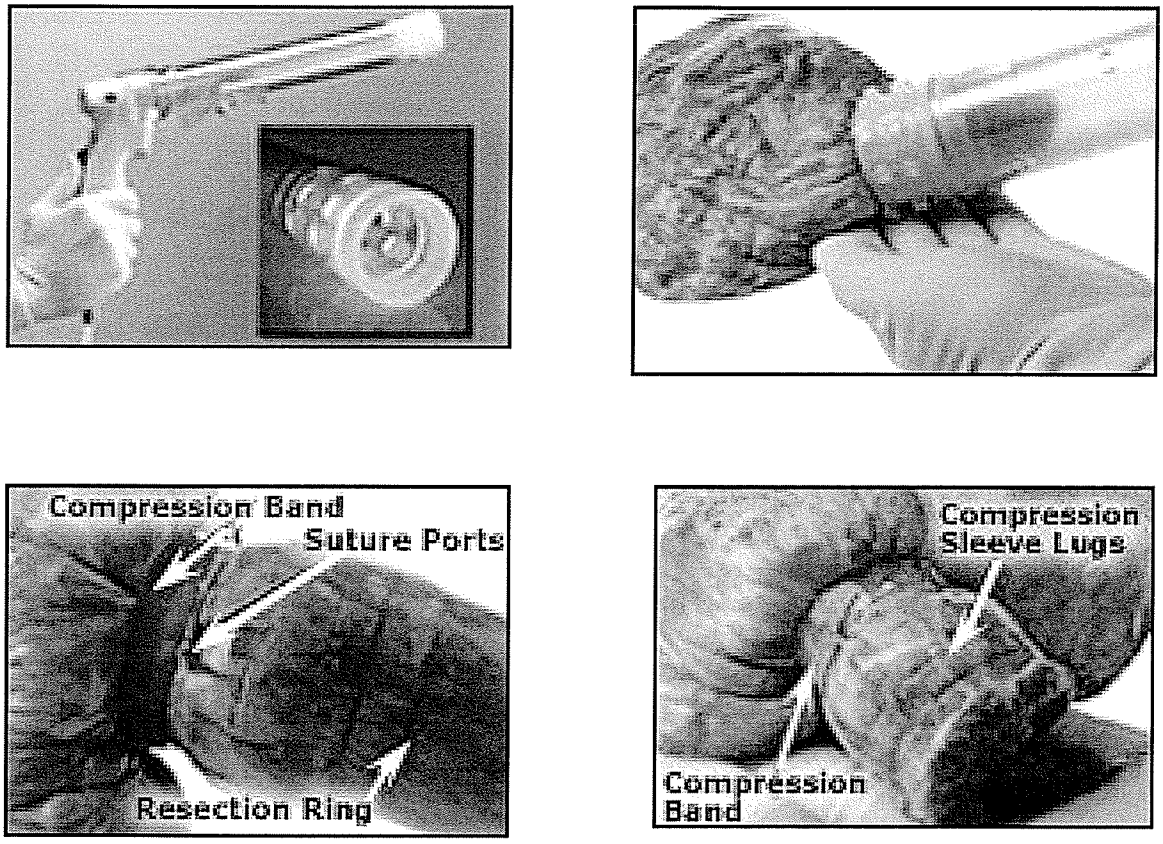


Figure 1. The lung volume reduction device (upper left panel) draws the tissue into the sleeve by vacuum suction (upper right panel). The sleeve containing the target lung tissue is excised after placing sutures at the compression band (lower left panel) and the excess lung is removed leaving the compression band in situ (right lower panel).

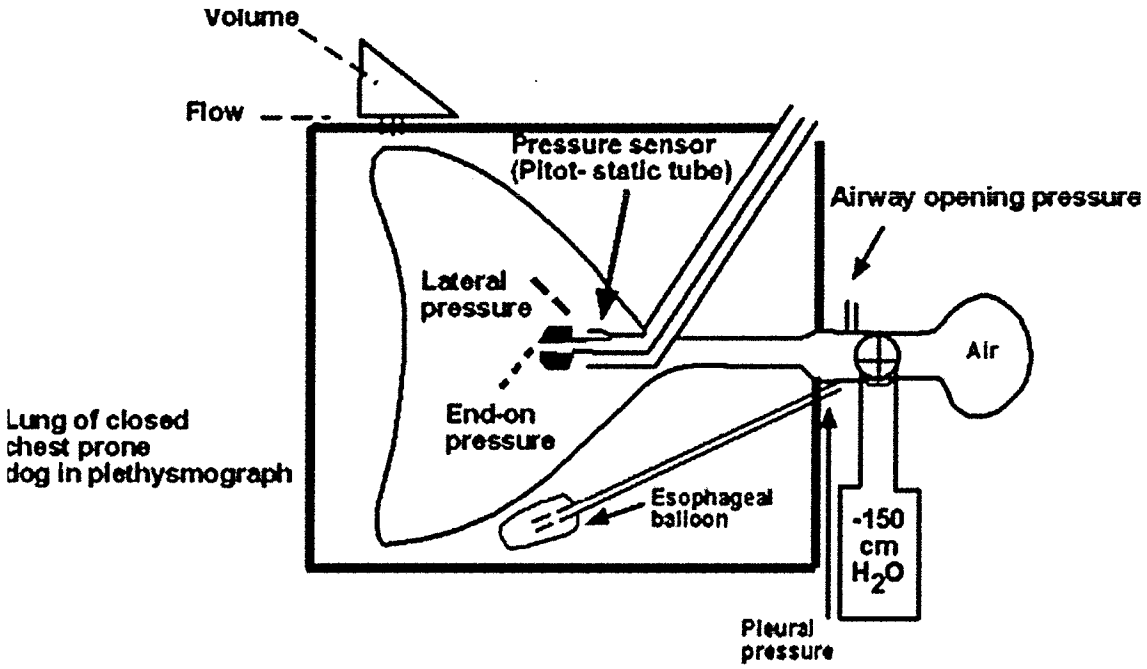


Figure 2: Schematic drawing of the apparatus for tests of parameters of maximal expiratory flow. The lungs are inflated to TLC and then the airway opened to a negative pressure reservoir to achieve maximal expiratory flow. Flow-volume curves and airway pressure-time curves were recorded during each forced deflation maneuver.

CHAPTER IV. RESULTS

A. PRE- LVRS

In the emphysema groups, the changes in lungs volume observed pre vs. post emphysema are shown in **Table 1** (see end of *Results: Pre-LVRS*). There was an approximately 20% increase in TLC in the combined emphysema groups post-papain administration, and RV and FRC showed similar findings. Oscillatory airway resistance and tidal lung compliance were not changed in the emphysema groups between baseline and post-emphysema measurements. Pressure-volume curves were performed in the emphysema groups before and after papain was administered. In this model of heterogeneous upper lobe emphysema, the post-emphysema curve was shifted upward and to the left and only slightly rotated as compared to the pre-emphysema curve (see **Figure 3**). In the present study, results were analyzed at 70%, 50%, and 30% of the VC. Performed in this manner, P_{el} in the emphysema group did not differ as compared with those found in the control group examined at 70%, 50%, and 30% VC (see **Table 2**).

Spirometry was reduced in the emphysema groups as compared with the control groups at all of the time intervals measured (see **Table 3**). In the control group, an example of a flow volume curve is delineated in **Figure 4** (left hand panel). As shown, V_{max} in the control dog remains constant for over most of the VC and then falls abruptly at approximately 30%VC. In the animal representative of the emphysema group (**Figure 4**, right hand panel), V_{max} is shown to peak at the high lung volumes, and then gradually decrease at the low lung volumes. On the mean, V_{max} in the emphysema groups were significantly less than corresponding values found in the control groups at the three lung volumes studied (see **Table 4**).

Choke-point locations were analyzed in terms of the geometry of the tracheobronchial tree in which a location in the trachea was described as generation 1, a location at the carina given as generation 2, etc. A schematic of the canine tracheobronchial tree is shown in **Figure 5**. On the mean, CPs in normal lungs were identified at the level of the trachea at 70% VC, at the level of the mainstem bronchus at 50% VC, and at the level of the lobar bronchus at 30% VC. In the emphysema groups, CPs at the two high lung volumes were generally found more upstream at the lobar bronchus. At 30%VC, CP in both emphysema and control groups were similarly located at lobar bronchi. The mean CP locations are shown in **Figure 5** in which the more upstream location of CP in the emphysema groups were of borderline significant difference as compared with the control group (P=0.06).

In the control groups, since the lungs were considered to empty homogenously during maximal flow, A* could be calculated whether CP were identified in the trachea or more upstream airways, since the flow subtended by the Pitot-Static was considered to be uniform among all similar sized airways. However, in the emphysema groups, expiratory flow would be nonhomogeneous, and A* could only be calculated when CP was identified at the level of the trachea. In the control groups, A* (see **Table 5**) averaged approximately 2.5 cm^2. In the emphysema groups, in the experiments in which A* could be calculated, A* averaged 1.5 cm^2 which was significantly less than that found in the control groups.

P_{fr} was calculated from P_{el}-P_{end}. With CP located at a more downstream site in the control groups, P_{fr} to CP were significantly higher than values measured in the emphysema groups (see **Table 6**). In those experiments in which CP were identified in the trachea, frictional resistance to CP was calculated from (P_{el}-P_{end})/Vmax, and there were no

differences between the two groups (see **Table** 7). In addition, in those experiments in which the CP was identified in the trachea, the transmural lateral pressure (P_{lat}) at the CP site was compared between the two groups. For these experiments, mean P_{lat} in the control group was more negative (-8.4 ± 0.7 vs. –4.3 ± 3.8 cm H_2O) than that found in the emphysema group, even though A* was smaller in the emphysema group.

Table 1. Lung volumes – Emphysema Group

	Pre-emphysema (n=9)	Post-Emphysema (n=9)
FRC (L)	0.83 ± 0.15	1.04 ± 0.34*
IC (L)	2.28 ± 0.38	2.61 ± 0.46*
TLC (L)	3.11 ± 0.46	3.65 ± 0.73*
RV	0.30 ± 0.12	0.51 ± 0.16*
VC	2.81 ± 0.42	3.14 ± 0.59*
ERV	0.52 ± 0.17	0.53 ± 0.19
R_L ($cmH_20/L/s$)	1.86 ± 0.97	1.85 ± 1.17
C_L (ml/cmH_20)	74 ± 17	76 ± 22
C_{cw} (ml/cmH_20)	84 ± 34	102 ± 27
C_{rs} (ml/cmH_20)	39 ± 4	42 ± 7

Values expressed as mean ± SD. TLC is total lung capacity; VC is vital capacity; IC is inspiratory capacity; RV is residual volume; ERV is expiratory reserve volume; FRC is functional residual capacity; R_L is oscillatory airway resistance; C_L is tidal lung compliance; C_{cw} is tidal chest wall compliance; C_{rs} is tidal compliance of the respiratory system. *P<.05 by paired t-test.

Table 2. Lung Elastic Recoil (in cmH_2O) in Post Emphysema and Control Groups at the three Vital Capacities (VC)

	VC_{70}	VC_{50}	VC_{30}
Emphysema groups (n=9)	5.6 ± 3.4	2.8 ± 2.5	0.7 ± 0.9
Control groups (n=8)	4.5 ± 2.2	1.7 ± 0.8	0.4 ± 0.7

Values expressed as mean ± SD. Measurements were obtained at 70%, 50% and 30% vital capacity (VC).

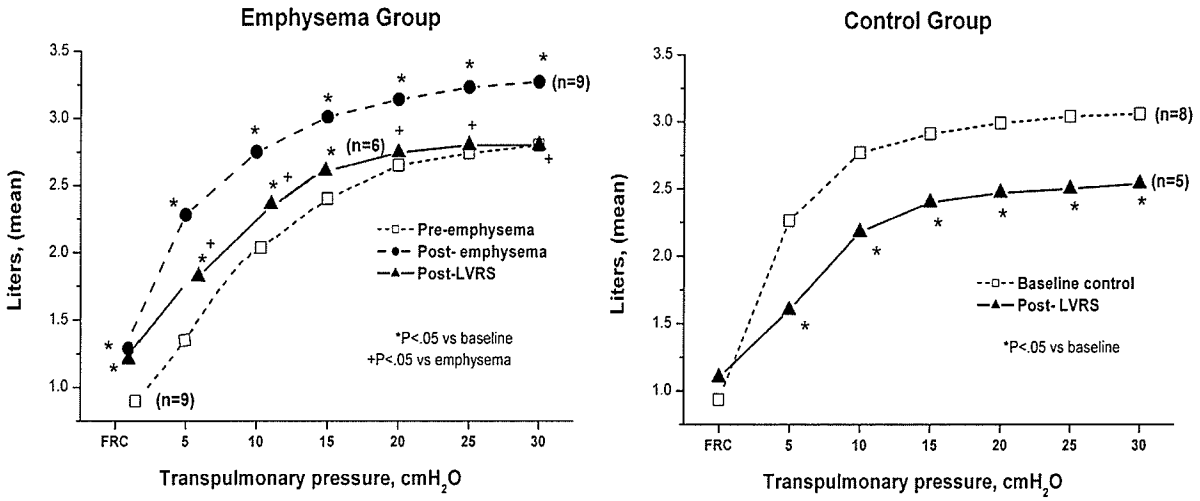


Figure 3. Volume-pressure curves obtained in the emphysema and control groups. Emphysema caused a upward and leftward shift in the curve as compared to the pre-emphysema curve. In both groups, after lung volume reduction surgery (LVRS), the curve was shifted downward and to the right. Statistics by two-way within-within analysis of variance.

Table 3. Forced Expiratory Volume (FEV) at various time intervals as percentage of Forced Vital Capacity (FVC) for Emphysema and Control Groups

	$FEV_{0.25}/FVC$	$FEV_{0.5}/FVC$	$FEV_{0.75}/FVC$	FEV_1/FVC
Emphysema Groups (n=9)	45 ± 9*	72 ± 7*	84 ± 4*	90 ± 2*
Control Groups (n=8)	64 ± 11	93 ± 5	97 ± 1	98 ± 1

Values are means $\pm$ SD in liters. *$p < 0.05$ between groups by two way between-within ANOVA

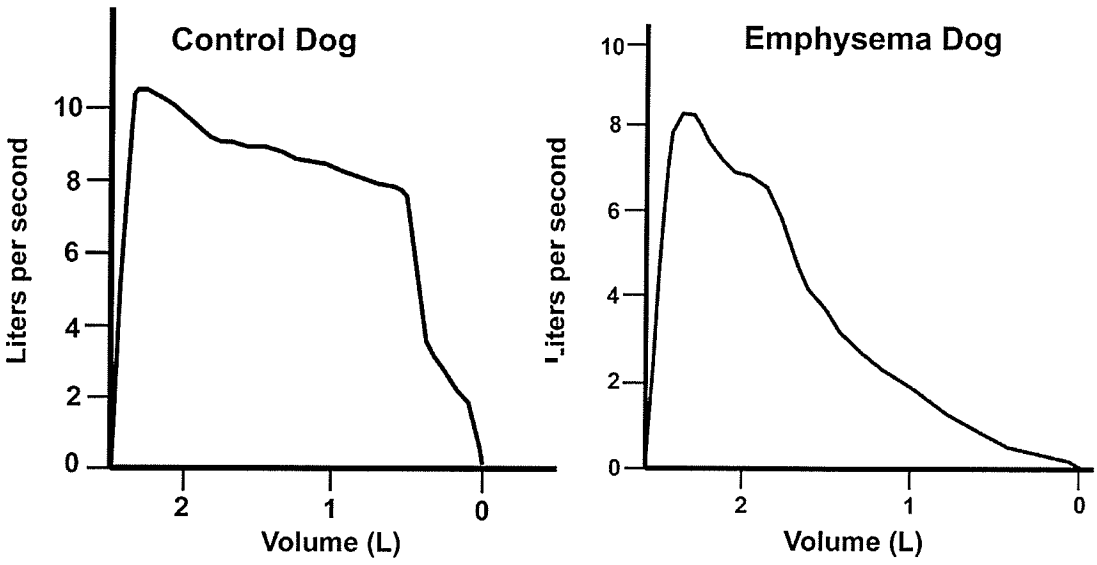


Figure 4. In the control dog (left hand panel), maximal flow remains high until approximately 20-30 % vital capacity and then decreases sharply. In the emphysema dog (right hand panel), maximal flow decreases gradually after peak flow is reached.

Table 4. Maximum Expiratory Flow (in L/S) for Post Emphysema and Control Groups at the three vital capacities (VC)

	VC_{70}	VC_{50}	VC_{30}
Emphysema (n=9)	6.4 ± 1.2*	5.1 ± 1.5*	2.8 ± 1*
Control (n=8)	8.7 ± 2	7.8 ± 1.6	6.3 ± 1

Values are means ± SD. *p < 0.001 between groups by two way between-within ANOVA

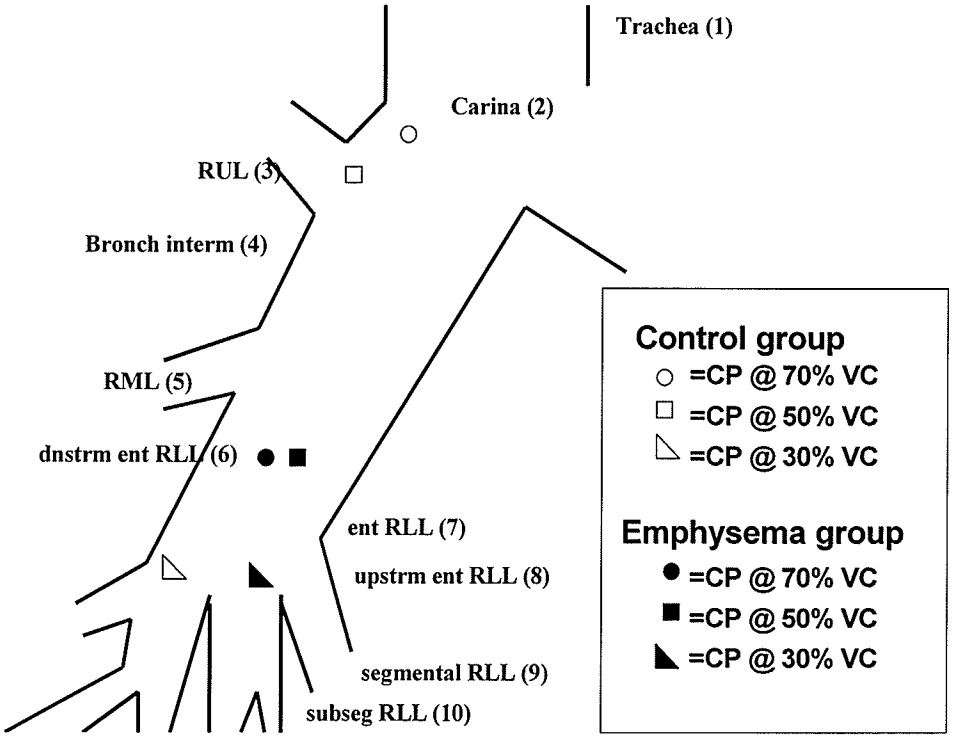


Figure 5. Mean Choke Point Locations Control, Emphysema Groups

In general, CPs of the control group were located centrally at high and mid lung volumes while CP in the emphysema groups were located peripherally. In the emphysema groups, mean (±SD) generations were 4.7 ± 3.9, 6.1 ± 4.0, 7.6 ± 1.8 vs in the control groups, 2.3 ± 1.2, 3.4 ± 2.1, and 6.6 ± 2.8 (P=.06 between groups).

Table 5. Bronchial Cross Sectional Area (in cm^2) in Emphysema and Control Groups

	VC_{70}	VC_{50}	VC_{30}
Emphysema	1.6 ± 0.4* (n=5)	1.5 ± 0.3* (n=3)	
Control	2.5 ± 1 (n=8)	3.2 ± 1 (n=8)	2.6 ± 0.9 (n=6)

Values are means ± SD in cm^2. Values in the emphysema group only included those in which choke points were identified in the trachea. In two dogs in the control groups, accurate pressure measurements could not be obtained at the low lung volume. *P<.05 between groups by two-way between-within ANOVA.

Table 6. Frictional pressure losses (in cm H_20) to the choke-point in Emphysema and Control groups

	VC_{70}	VC_{50}	VC_{30}
Emphysema	1.9 ± 2.7* (n=9)	1.5 ± 2.2* (n=9)	0.8 ± 1.7* (n=9)
Control	4.0 ± 2.25 (n=8)	4.5 ± 2.2 (n=8)	3.6 ± 2.6 (n=7)

Values are means ± SD. *P<.05 between groups by two way between within ANOVA

Table 7. Frictional resistance (in cmH_20 / L/s) to the choke-point in Emphysema and Control groups

	VC_{70}	VC_{50}	VC_{30}
Emphysema	0.34 ± 0.41 (n=5)	0.34 ± 0.46 (n=3)	
Control	0.51 ± 0.38 (n=8)	0.63 ± 0.4 (n=8)	0.58 ± 0.54 (n=7)

Values are means ± SD. Values in the emphysema group only included those in which choke points were identified in the trachea.

B. POST-LVRS

In the emphysema group, after LVRS was performed, TLC, VC, and IC in the emphysema group returned near to pre-emphysema values (see **Table 8**), while FRC and RV remained unchanged as compared with pre-LVRS values. The fact that RV remained unchanged post-surgery, while TLC decreased indicates that gas trapping increased postoperatively. RV/TLC was used as a marker of gas trapping and this fraction increased after LVRS. In addition, respiratory system compliance decreased post-surgery, which was predominantly due to a decrease in tidal chest wall compliance, although tidal lung compliance decreased to some extent. In the control group, similar changes in lung volumes and mechanics were observed after surgery, and evidence of gas trapping and reduced tidal respiratory compliance was observed.

In the emphysema and control groups, the pressure-volume curves obtained after LVRS are shown in **Figure 3**. The curves were shifted downward and to the right as compared with the respective pre-surgery curves. For similar fractions of the VC obtained pre vs. post LVRS, P_{el} were generally higher post-LVRS. Following LVRS, P_{el} increased at the two highest lung volumes in both the control and emphysema groups, while P_{el} also increased at the lowest lung volume in the emphysema group (see **Figure 6**).

Following LVRS, the ratios of FEV/FVC increased in the emphysema group, while FEV/FVC ratios were unchanged post-LVRS in the control group. When compared to the control group, the increases in FEV/FVC ratios for the emphysema group found after LVRS were statistically significant as compared to the results found in the control group (see **Table 9**).

Pre-LVRS, V_{max} in the emphysema group were significantly lower at all lung volumes as compared with the control group. Following LVRS, V_{max} in the emphysema group decreased at the two higher lung volumes as compared with pre-LVRS, while V_{max} was slightly increased at the lowest lung volume. Post-LVRS, V_{max} at VC_{30} in the control group decreased as compared with pre-LVRS, and this finding was significantly different from that found in the emphysema group (see **Figure 7**).

After LVRS, CPs were identified to determine whether movement occurred after lung resection. In five of the six emphysema dogs, CP moved downstream, while in one dog, CP moved upstream; in the control group, in three dogs, CP moved downstream, while in one dog, CP moved upstream; in the other dog, CP did not change. On the mean, CP movement was small and was non-significantly different between groups (see **Table 10**).

P_{fr} and resistance to CP were compared between the control and emphysema groups before and after LVRS was performed. In both groups, LVRS was associated with a tendency for P_{fr} and frictional resistance to increase as compared to pre-surgery (see **Tables 11 & 12**). The values for transmural P_{end} pre- and post-LVRS in the control and emphysema groups are shown in **Table 13**. P_{end} in the emphysema group were higher than those found in the control group, but there was no effect of LVRS on this parameter.

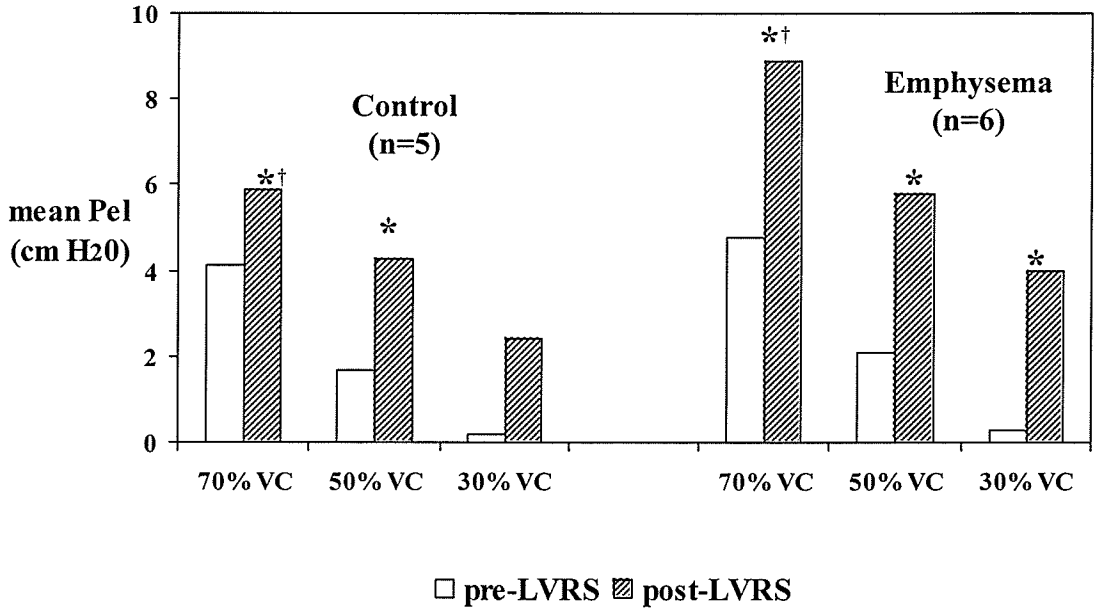
A* are shown for pre- and post-LVRS in the emphysema and control groups in **Table 14**. A* in the emphysema group were significantly lower that those in the control group, but there was no effect on LVRS on these findings. Transmural P_{lat} values in the control group were significantly more negative than those found in the emphysema group, while no effect of LVRS on P_{lat} was observed (see **Table 14**).

Table 8. Lung volumes and tidal compliances pre and post LVRS

	EMPHYSEMA		CONTROL	
	Pre-LVRS (n=6)	**Post-LVRS (n=6)**	**Pre-LVRS (n=5)**	**Post-LVRS (n=5)**
FRC (L)	1.14 ± 0.35	1.1 ± 0.3	0.82 ± 0.12	0.9 ± 0.17
IC (L)	2.7 ± 0.5	2.1 ± 0.7*	2.7 ± 0.5	2.02 ± 0.41*
TLC (L)	3.86 ± 0.8	3.1 ± 0.7*	3.5 ± 0.6	2.92 ± 0.55*
RV (L)	0.56 ± 0.17	0.65 ± 0.3	0.45 ± 0.1	0.44 ± 0.05
VC (L)	3.3 ± 0.6	2.5 ± 0.7*	3.1 ± 0.5	2.48 ± 0.55*
ERV (L)	0.58 ± 0.19	0.41 ± 0.06	0.4 ± 0.1	0.47 ± 0.17
R_L ($cmH_20/L/s$)	2.05 ± 1.41	3.44 ± 4.16	1.3 ± 0.2	1.0 ± 0.3
C_L(ml/cmH_20)	74 ± 22	66 ± 13	73 ± 20	72 ± 18
C_{cw}(ml/cmH_20)	115 ± 21	85 ± 32	102 ± 21	77 ± 43
C_{rs}(ml/cmH_20)	43 ± 8	36 ± 8*	40 ± 4	34 ± 13*
RV/TLC%	14 ± 2	22 ± 10*	13 ± 1	15 ± 3*

Values are means ± SD. *$p < 0.05$ pre- vs. post-LVRS by between-within ANOVA.

Figure 6. P_{el}: Control vs. Emphysema Groups Following LVRS



*p<0.05 compared to pre-LVRS P_{el}

†p<0.01 between control & emphysema groups by ANOVA

Table 9. Forced expiration volume (FEV) at various intervals as a percentage of forced vital capacity (FVC) pre-and post-LVRS for Emphysema and Control Groups

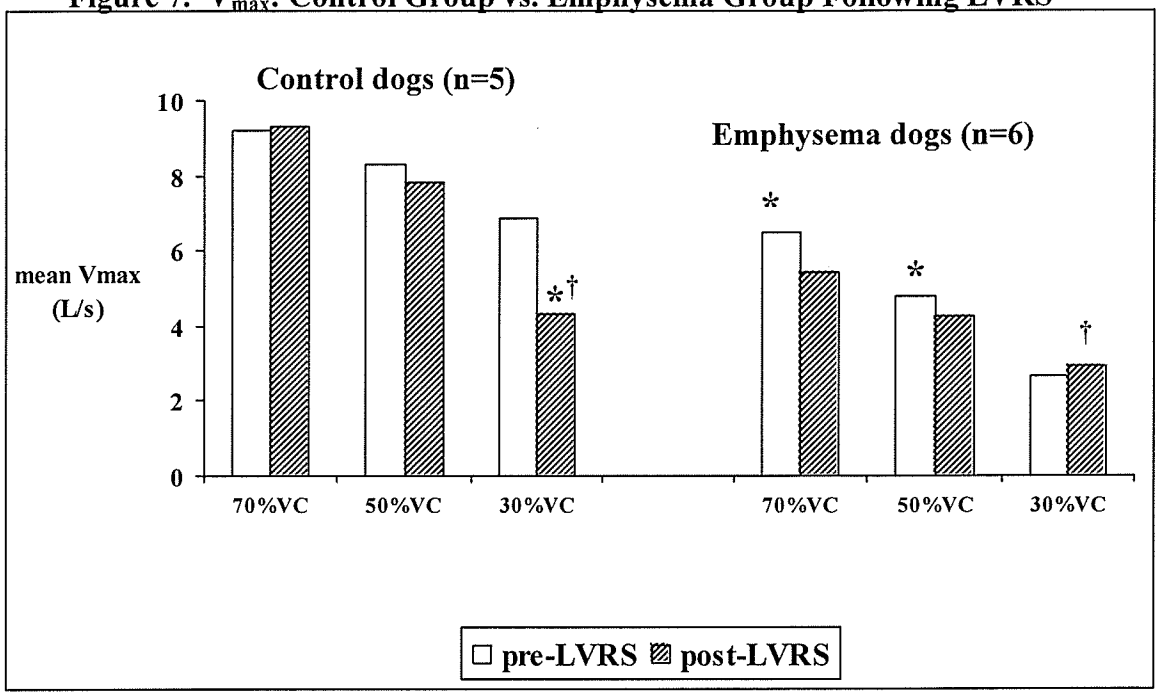
		$FEV_{0.25}/FVC$	$FEV_{0.5}/FVC$	$FEV_{0.75}/FVC$	FEV_1/FVC
Control (n=5)	**Pre-LVRS**	66.5 ± 6.5	95.5 ± 0.5	97.6 ± 0.8	98.4 ± 0.55
	Post-LVRS	70.8 ± 5.23	94.5 ± 1.96	97.8 ± 0.81	98.7 ± 0.83
Emphysema (n=6)	**Pre-LVRS**	42.2 ± 9.3*	70.1 ± 6.9*	83.2 ± 3.7*	89.5 ± 2.7*
	Post-LVRS	49.2 ± 10.5**	76.2 ± 9.8**	89.0 ± 6.3**	94.2 ± 4.0**

Values expressed as mean ± SD

*p<0.0001 compared to control group pre LVRS values by ANOVA

**p<0.01 compared to control group post LVRS difference by ANOVA

Figure 7. V_{max}: Control Group vs. Emphysema Group Following LVRS



Values expressed as mean ± SD in L/s

*P<.05 vs pre-LVRS by three way ANOVA; †P<.05 between groups.

Table 10. Change in choke-point airway generation (pre-LVRS – post-LVRS) in emphysema and control groups

	VC_{70}	VC_{50}	VC_{30}
Emphysema (n=6)	0.8 ± 3.1	1.2 ± 4.5	2.25 ± 4.3
Control (n=5)	-1 ± 1.6	-3.2 ± 4.3	1.4 ± 2.9

Values expressed as mean ± SD

Table 11. Frictional pressure losses to the choke-point (in cmH_20) pre- and post-LVRS in Emphysema and Control groups

		VC_{70}	VC_{50}	VC_{30}
Emphysema (n=6)	Pre-LVRS	1.3 ± 4.5	1.3 ± 3.5	0.05 ± 1.3
	Post-LVRS	3.8 ± 3.2	3.8 ± 2.9	4.4 ± 3.3
Control (n=5)	Pre-LVRS	3.7 ± 2.8	4.7 ± 2.5	1.5 ± 3.5
	Post-LVRS	5.8 ± 2.2	4.2 ± 3.2	1.9 ± 1.4

Values expressed as mean ± SD

Table 12. Frictional resistance (in $cmH_20/L/s$) to the choke-point pre- and post-LVRS in Emphysema and Control groups

		VC_{70}	VC_{50}	VC_{30}
Emphysema	**Pre-LVRS**	0.38 ± 1.02 (n=3)	0.94 ± 0.23 (n=2)	
	Post-LVRS	0.66 ± 0.56* (n=6)	0.71 ± 0.42* (n=6)	1.13 ± 1.17 (n=6)
Control	**Pre-LVRS**	0.42 ± 0.35	0.59 ± 0.36	0.20 ± 0.52
	Post-LVRS	0.69 ± 0.31* (n=5)	0.55 ± 0.39* (n=5)	0.53 ± 0.35* (n=4)

Values expressed as mean ± SD. Pre-LVRS values in the emphysema group only included those in which choke points were identified in the trachea.
*P=.05 Pre- vs. post-LVRS by three way ANOVA

Table 13. End-on transmural pressures at the choke-point (in cmH_20) pre- and post-LVRS in Emphysema and Control groups

		VC_{70}	VC_{50}	VC_{30}
Emphysema (n=6)	Pre-LVRS	3.5 ± 4.2*	0.3 ± 3.3*	-0.6 ± 2.4*
	Post-LVRS	5.5 ± 6.0*	2.4 ± 4.4*	0.4 ± 2.9*
Control (n=5)	Pre-LVRS	0.42 ± 1.6	-3.1 ± 1.8	-1.1 ± 3.0 (n=4)
	Post-LVRS	0.14 ± 2.9	0.06 ± 3.3	0.8 ± 1.6

Values expressed as mean ± SD
*P=.05 Emphysema vs. control groups by three-way ANOVA

Table 14. Cross-sectional area at the choke-point (in cm^2) pre- and post-LVRS in Emphysema and Control groups

		VC_{70}	VC_{50}	VC_{30}
Emphysema	Pre-LVRS	1.5 ± 0.4* (n=3)	1.5 ± 0.4* (n=2)	
	Post-LVRS	1.5 ± 0.4* (n=6)	1.35 ± 0.6* (n=6)	1.4 ± 0.6* (n=5)
Control	Pre-LVRS	2.5 ± 0.9 (n=5)	3.4 ± 1.0 (n=5)	2.7 ± 0.9 (n=3)
	Post-LVRS	2.9 ± 0.4 (n=5)	4.4 + 2.0 (n=5)	2.0 ± 0.8 (n=5)

Values expressed as mean ± SD
*P<.05 Emphysema vs. control groups by three-way ANOVA

Table 15. Lateral transmural pressures at the choke-point (cmH_20) pre- and post-LVRS in Emphysema and Control groups

		VC_{70}	VC_{50}	VC_{30}
Emphysema Group (n=6)	Pre-LVRS	-4.5 ± 4.1*	-4.1 ± 3.5*	-2.4 ± 2.5*
	Post-LVRS	-2.5 ± 3.9*	-2.6 ± 4.2*	-0.8 ± 4.0*
Control Group (n=5)	Pre-LVRS	-7.6 ± 1.6	--7.2 ± 2.5	-4.2 ± 2.1 (n=4)
	Post-LVRS	-5.6 ± 1.5	-2.4 ± 4.1	-3.3 ± 3.6

Values expressed as mean ± SD
*P<.05 Emphysema vs control groups by three-way ANOVA

C. TIME- CONTROL EXPERIMENTS

Three emphysema and three control dogs were followed over the interval of the study to determine whether parameters of maximum flow at the end of the study in non-LVRS treated animals would be comparable to those found prior to surgery in the LVRS study.

In the emphysema dogs, at the end of the study, there was a comparable increase in TLC as that found in the LVRS emphysema group from 2.87 ± 0.22 L pre-emphysema to 3.24 ± 0.19 L after emphysema. P_{el} examined at the three volumes in the emphysema group (7.1 ± 4; 4.2 ± 3.13; 1.5 ± 1.2 cm H_20) were not different from those found in the control group (5.1 ± 1; 2.2 ± 0.3; 0.03 ± 0.06 cmH_20). V_{max} in the emphysema dogs at the three lung volumes examined (6.1 ± 1.8, 5.7 ± 1.4, 3.2 ± 0.9 L/s) were also comparably lower than those found in the control dogs (7.7 ± 1.9; 7.2 ± 1.6; 6.4 ± 1.3 L/s). CPs were identified at airways comparable to those found in the LVRS groups (airway generation 2.8 ± 1.6; 6.3 ± 4.7; 7 ± 2.6 in the emphysema group vs. 2.2 ± 2.1; 3.3 ± 2.1; 6 ± 4 in the control group). When CP were found in the trachea, A* in the emphysema group were lower than those measured in the control group in a manner similar to that found in the LVRS groups (1.6 ± 0.53 (n=2); 1.4 (n=1) cm^2 vs. 2.3 ± 1.2; 2.8 ± 1.2; 2.4 ± 0.5 cm^2).

Moreover, in the three experiments in the control group, V_{max} and CP variables were repeated approximately one month between studies in an attempt to determine whether the parameters could be reproducibly obtained. Parameters were very similar on the two occasions. Among the variables determined, V_{max} measured 7.9 ± 2.4; 7.0 ± 1.7; 5.4 ± 1.2 L/s initially vs. 7.7 ± 1.9; 7.2 ± 1.6; 6.4 ± 1.3 L/s at the second study; P_{el} measured 5.3 ± 2.6, 1.8 ± 0.7, 0.7 ± 1.2 at the initial study vs. 5.1 ± 1, 2.2 ± 0.3, 0.03 ± 0.06

cm H_20 at the second study. CP airway generations were 2.2 ± 1.3; 4.5 ± 3.1; 5 ± 3 vs. 2.7 ± 2.1; 3.3 ± 2.1; and 6 ± 4. A* were 2.5 ± 1.5; 3.1 ± 1.2; 2.4 ± 1.1 cm^2 at the initial study vs. 2.3 ± 1.2; 2.8 ± 1.2; 2.4 ± 0.5 cm^2 at the second study.

CHAPTER V: DISCUSSION

In the present study, the acute effects of LVRS on parameters of maximal expiratory flow and lung mechanics in an upper lobe model of emphysema were studied. The findings of emphysema per se on parameters of expiratory flow limitation were similar to those previously reported. The results showed evidence of hyperinflation and air trapping as well as a decrease in spirometry and expiratory flows. However, in contrast to what was observed in a diffuse emphysema model in which papain was instilled into all of the lung lobes, in this predominantly upper lobe model, it was observed that when P_{el} were examined at similar fractions of the VC, P_{el} were unchanged as compared with the control group. This can be ascribed to the more localized nature of the lesion in which the effect of papain on lung elastic recoil was less apparent as compared to the diffuse model, and because the major physiological effect of papain is to increase air trapping rather than to decrease elasticity. The net effect of papain on the volume-pressure curve in emphysema was to shift the curve in a parallel manner upward and to the left as compared to the non-emphysema curve (see **Figure 3**).

In terms of forced expiration, the major determinants of V_{max} have been discussed and include P_{el}, P_{fr} and bronchial airway pressure behavior. Since P_{el} were not different at the three lung volumes examined between the emphysema and control groups, the mechanism of the decrease in V_{max} observed in the emphysema group must be related either to an increase in P_{fr} or to a more compliant airway. In both groups, P_{fr} were calculated at the three lung volumes, and the results were found to be lower and not higher

in the emphysema group. Nevertheless, this finding must be considered in the context of different CP locations between the two groups. At 70% and 50%VC, CP in the control groups were identified slightly downstream to those determined in the emphysema group. Thus, a direct comparison of P_{fr} is difficult to ascertain, since the longer airway to CP would be expected to be associated with greater P_{fr} in the control group. Nevertheless, at 30%VC, CP in both groups were identified at lobar bronchi where P_{fr} if anything were still lower in the emphysema group. Thus, an increase in P_{fr} does not appear to explain the reduction in V_{max} found in the emphysema group.

The mechanism of the decrease in V_{max} measured in the emphysema group appears best explained by an alteration in bronchial pressure airway behavior. In pulmonary emphysema, as parenchymal destruction occurs, a more compliant airway may develop as a result of a loss of bronchial tethering and/or due to a decrease in longitudinal tension. Then, for a given transmural pressure, airway cross-section would be reduced after emphysema is produced. This mechanism was found to be important in a model of diffuse papain-induced emphysema where only a part of the decrease in V_{max} observed could be explained by a reduction in P_{el}, while the remainder was due to altered airway behavior.[63] Similarly, such a change in bronchial pressure area behavior appears to have played a role in the present study. In the emphysema group, when CP were identified in central airways, A* were found to be lower than in the control group, even though transmural pressures were more positive in the emphysema group. In the present study, this would be consistent with a change in bronchial pressure area behavior limiting flow at a lower V_{max} in the emphysema groups.

After LVRS, TLC decreased approximately 20% as compared with pre-surgery in both groups, and in particular, TLC approximated the pre-emphysema value in the emphysema group. Although significant reductions in TLC were observed, FRC and RV were not reduced, and in some case remained slightly higher as compared to the pre-surgery values. The ratio of RV/TLC increased in both groups, and this finding would support the notion that a relative increase in air trapping occurred after surgery. Thus, after acute LVRS, the subdivisions of lung volumes are not proportionally reduced and air trapping was observed leading to a relatively higher RV and FRC than was expected.

Post-LVRS, the static deflation volume-pressure curves were shifted downward and rotated to right as compared with pre-surgery in both the emphysema and control groups. Part of the rationale of performing LVRS is to remove emphysematous units, since this removal would increase overall lung recoil and improve lung mechanics. In the present study, the pressure-volume curve in the emphysema groups was shifted upward and to the left as compared with the pre-emphysema curve. Yet the overall shape of the curve was basically unchanged as compared with the pre-emphysema curve and the predominant effect of papain was to cause air trapping. Removal of emphysematous lung units after surgery would be expected to shift the curve back to the pre-emphysema curve. However, this was the case only at the very high lung volumes, while at the mid-lower lung volumes, at a given fraction of the VC, P_{el} appeared higher in the post LVRS curve. This effect can also be seen in the control group. Although removal of normal lung units would be expected to reduce TLC, at the same fractions of VC, P_{el} should be the same pre- vs. post-surgery in the control group, since overall elasticity of the remaining units would be

unchanged between conditions. However, in both the control and emphysema groups, for similar fractions of the VC, P_{el} increased after surgery.

The mechanism of the increase in P_{el} after LVRS was probably multifactorial. In one aspect, since air trapping relatively increased after surgery, as indicated by an increase in RV/TLC, airway closure may occur at a higher fraction of the VC. This effect could decrease the number of lung units contributing to the expirate during deflation. For a given gas volume, a reduction in the number of lung units would increase P_{el}. In addition, an increase in P_{el} could reflect altered properties of the alveolar units themselves. Changes in surfactant leading to an increase in P_{el} could occur related to manipulation of the lung tissue and/or the high oxygen concentrations used during the procedure.

Nevertheless, an increase in P_{el} would be expected to lead to a higher V_{max} post LVRS. In terms of wave-speed theory, with CP located at the same airway generation (which on the mean was essentially found for both groups in the present study), a higher P_{el} would ordinarily increase the pressure head (i.e. end-on pressure) at the CP. This would be expected to result in a higher A* and hence a higher V_{max} during forced expiration. However, as compared with pre-LVRS, it was observed that in the emphysema group V_{max} decreased at the higher two lung volumes, while in the control group, V_{max} decreased at the lowest lung volume. In order to determine the effect of LVRS on the wave-speed determinants, P_{end} were measured at the three lung volumes before and after LVRS in the emphysema and control groups. P_{end} did not systematically increase, and indeed decreased at some lung volumes, while on the mean, the net effect was an unchanged P_{end} in both groups (see **Table 13**).

The lack of an increase in P_{end} post-LVRS indicates that there may have been greater dissipation of frictional pressure losses to CP, since P_{el}-P_{fr} = P_{end}. In **Table 11**, this was generally the case, in which P_{fr} appeared to increase post-LVRS, particularly in the emphysema group. Frictional resistance to CP was also generally higher post-LVRS (see **Table 12**), again supporting the view that an increase in P_{fr} offset the increase in P_{el}, such that V_{max} did not increase post-LVRS.

The net consequence of LVRS on V_{max} will be dependent upon the extent to which the increases in P_{el} and P_{fr} offset one-another at each lung volume. In the emphysema group, at the two highest lung volumes, since V_{max} decreased, this would suggest that the major effect was an increase in P_{fr}. On the other hand, at the lowest lung volume, the effect of the increase in P_{el} was equal or slightly greater than the increase in P_{fr}, so that V_{max} did not change after surgery and in fact was slightly higher post-LVRS. In the control group, at the lowest lung volume, the increase in P_{fr} outweighed the effect of the increase in P_{el}, so that V_{max} decreased after LVRS. The mechanism of the increase in P_{fr} and airway resistance following LVRS is speculative. This increase in airway resistance could be related to bronchoconstriction secondary to handling of the parenchyma, compression of the airways as a consequence of changes in lobar geometry when the chest wall was closed, or to airway secretions. In addition, it is possible that torsion of the airways may have occurred increasing resistance when the chest was closed.

Another important factor to consider is that after LVRS, a decrease in tidal compliance of the respiratory system was also observed in both the emphysema and control groups. For the most part, this decrease reflected a reduction in chest wall compliance, while lung compliance decreased only slightly. The mechanism of this decrease was

probably related to upward movement of the diaphragm into the chest cavity that made the pressure volume behavior of the chest-wall and diaphragm stiffer. In clinical medicine, such an effect would lead to an increase in the work of breathing and would contribute to a difficult weaning process after LVRS is performed.

In this study, parameters of flow limitation were determined at 70%, 50% and 30% of the VC measured at each study interval. In terms of this analysis, such an approach may have affected interpretation of the results, since absolute lung volumes examined were not the same at each study interval. Some discussion about this analysis is warranted. The rationale for using the present analysis was that it is the one most commonly used in clinical medicine[32]. Nevertheless, it should be noted that when analyses were performed either at the same absolute lung volumes from TLC pre- and post-LVRS or as a percentage of baseline lung volume for the non-emphysema group, the overall conclusions of the study would not change to a large extent. For instance, in the emphysema group, consider the findings if the results were analyzed at the same absolute lung volume from TLC pre- vs. post-LVRS. Then, the fractions of VC examined post-LVRS would be lower compared to those determined in the present analysis, since the absolute volume as measured from TLC would have been greater than before. In that case, the effects on parameters of flow limitation would be as follows. From the pressure-volume curves shown in **Figure 3**, the increase in P_{el} found post-LVRS would not have been as large as compared to the present analysis, since the volume analyzed would now occur at lower fractions of the VC following surgery where P_{el} would have been lower. However, the decreases in V_{max} found post-LVRS would be much greater than those determined by the present analysis, since from the flow-volume curve, V_{max} at these lower fractions of the VC would also have been

lower. Accordingly, the major conclusion of the study would be the same regardless of the analysis undertaken showing that V_{max} did not increase immediately following LVRS in this emphysema model.

Another interesting finding in this study is that in the emphysema group, although V_{max} decreased at 70%VC and 50%VC post-LVRS as compared to pre-surgery, FEV/FVC% measured at the different time intervals were higher following surgery (see **Table 9**). These increases in spirometry post-LVRS probably reflected the effect of the slightly higher V_{max} found at the lowest lung volume, since in the normal canine lung, 70% of the expirate empties in the first 0.25s. On the other hand, the lower values of Vmax observed at 70%VC and 50%VC post-LVRS in the emphysema group would have been reflected at intervals <0.25s . In the human lung, in which it takes approximately 1 second for the lung to empty 70% of the expirate, changes in V_{max} that occur at the initiation rather than at end of the expiration would play more of a role in determining these spirometry values. Thus, the relevance of the present findings to the human condition needs to be interpreted cautiously. Nevertheless, in clinical medicine, spirometry changes are often interpreted as success of the LVRS procedure. The present study shows that an increase in spirometry does not necessarily indicate that beneficial mechanical changes have actually occurred post-LVRS.

Whereas most investigators have centered on the long-terms effects of LVRS on lung mechanics and V_{max}, there is only limited information about changes that evolve in the immediate post-operative period. Barnas et al[60] examined the acute effects of LVRS on lung and chest wall mechanical properties in patients. These investigators reported results similar to those found in the present study, in that airway resistance increased and

respiratory compliance decreased post-surgery. Although maximum expiratory flow was not examined in the latter study, both the present study and that of Barnas et al show that the acute changes in lung mechanics that occur after LVRS may hinder the weaning of patients from the ventilator in the immediate post-operative period.

The effects of acute LVRS differ from those previously reported in a previous study in which this technique of LVRS was used in a model of upper lobe emphysema and in which the results were evaluated at 1 month and 6 months post-surgery.[29] In this chronic study, respiratory compliance did not decrease at the time intervals measured, and the pressure-volume curve determined at one month post surgery in the emphysema group could be superimposed on that found pre-emphysema. In contrast to the present study, in a previous study, V_{max} after LVRS increased at 50% VC as compared with the pre-surgery in this emphysema model. These results point out that the changes in lung recoil and airway resistance found after surgery are transient and that over time remodeling leads to more beneficial effects of this treatment on lung mechanics.

The present study points out that the changes in lung mechanics and V_{max} following LVRS is a complex process. These involve both acute changes and a more chronic parenchymal and airway remodeling processes. In the present study, we demonstrated that LVRS resulted in 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 mortality, particularly in patients who have very severe emphysema. Significant improvements in parameters of maximal flow and lung mechanics may not occur until some time has passed during which changes in airway and lung remodeling may occur. Based on previous work in this model,

improvements in lung function after LVRS occur at the 1-month interval. Enhanced knowledge of the complex mechanisms involved in LVRS will ultimately lead to better patient selection for the procedure.

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