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An Animal Model for Lung Volume Reduction Therapy of Pulmonary Emphysema

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ABSTRACT Stapled lung volume reduction surgery (LVRS) has recently been described for treatment of emphysema. Many questions arise regarding physiologic mechanisms of response from surgical treatment of emphysema. The objective of this study was to develop an animal model for the study of lung volume reduction surgery in diffuse heterogeneous emphysema. We hypothesized that elastic recoil would increase, static respiratory system compliance would decrease, and expiratory flows would increase after lung volume reduction surgery in animals with emphysema. In the study, emphysema was induced in 31 New Zealand White rabbits (3–5 kg) with endotracheally aerosalized porcine elastase (10,000–12,000 U). Lateral thoracotomies were performed 4–6 weeks postinduction under general anesthesia and mechanical ventilatory support. Stapled volume reduction was performed on the right lower lobe using a standard multirow pediatric stapler (U.S. Surgical). Pulmonary function tests were performed at baseline (preinduction), before stapling LVRS (postemphysema induction), immediately post stapling LVRS, and 1 week poststapling. Static respiratory system compliance, flow, conductance and forced expiratory flows, and peak flows at 20 and 40 cm^3 of exhaled volume were analyzed. Animals were sacrificed 1 week poststapling, and bilateral lungs were harvested for histopathology. Diffuse but heterogeneous pulmonary emphysema was seen in these animals treated with high-dose aerosolized elastase. Static compliance increased, while expiratory flows and conductance decreased after induction of emphysema. Immediately post stapled volume reduction therapy, animals had decreased static compliance. By 1 week following surgery, animals showed increased forced expiratory flows and decreased expiratory resistance, although compliance was similar to preoperative levels. In conclusion, we describe initial results in an animal model of obstructive emphysema suitable for the study of lung volume reduction surgery. Changes in pulmonary function indicate that unilateral lower lobe LVRS increases airway conductance in the rabbits. Findings from LVRS studies in animal models such as this may help explain clinical improvement following LVRS in humans.

KEYWORDS emphysema, rabbit, LVRS, volume reduction, animal

Medical therapy has limited benefit for patients with advanced emphysema. More than 35 years ago, Dr. Otto Brantigan [1] reported his experience with partial lung resection in patients with diffuse pulmonary emphysema. He hypothesized that in chronic obstructive pulmonary disease (COPD), patients with distended lungs lose the normal outward circumferential pull on the bronchioles, causing collapse during expiration [1]. He proposed that reducing overall lung volume, by means of multiple wedge excisions, would restore the outward elastic pull on the small airways and reduce expiratory airway obstruction.

Recently, Cooper et al. [2,3] reported bilateral lung volume reductions in patients with severe chronic obstructive pulmonary disease with relief of thoracic distention and improvement in respiratory mechanics.

Numerous questions remain concerning lung volume reduction surgery (LVRS) regarding efficacy, optimal surgical techniques, mechanisms and duration of response, selection criteria, and economic impact of the procedure. Animal LVRS models are needed to evaluate surgical treatment of emphysematous lung disease.

The purpose of this study is to describe development of an animal model of diffuse obstructive emphysema suitable for the study of LVRS, and to demonstrate the potential for evaluating physiologic response to lung volume reduction.

MATERIALS AND METHODS

Induction of Emphysema

This protocol was approved by the AALAC-approved Animal Research Committee at our institution in compliance with state and federal regulations.

Emphysema was induced in male New Zealand White rabbits by a single nebulization of porcine elastase into the airways following endotracheal intubation. Prophylactic antibiotic, Baytril at 0.22 mg/kg im, was administered preinduction. Rabbits (3–5 kg) were anesthetized using inhaled isoflurane 5%, followed by 0.2 cm^3 ketamine/xylazine in a 1:1 mixture via intravenous injection. Rabbits were intubated over a guide wire with a 3.0–3.5-mm cuffed pediatric endotracheal tube under direct visualization using a number 1 straight-blade laryngoscope. Porcine pancreatic elastase at 10,000–12,000 U (ICN Biomedicals, Inc., activity 3750 U/mL, Aurora, OH) in 3 cm^3 normal saline was aerosolized (Respirgardô, Marquest Medical Products, Inc., Englewood, CO) over 20–40 min. Sedation was maintained with a 1:1 mixture of ketamine HCl (100 mg/ml) and xylazine (20 mg/ml). Ventilatory support was provided by a Harvard ventilator (Harvard Apparatus dual phase control respiratory pump–canine, Harvard Co., South Natic, MA) set at a tidal volume of 40 ml, frequency of 20–30/min (adjusted to keep pCO_2 between 30 and 35), after inflation of the cuff with 1–2 cm^3 of air.

PULMONARY MECHANICS

Pulmonary Function Testing

Static Respiratory System Compliance

Pressure–volume curves were determined under static conditions with animals in the left lateral decubitus position and apnea maintained with intravenous injections of 1:1 ketamine/xylazine.

To avoid error due to variable volume history, the lungs were initially inflated to 80 ml above the functional residual capacity (FRC). After allowing the lungs to return to FRC, they were inflated to 60, 50, 40, 30, and 20 ml while the transpulmonary pressures were measured. The state of inflation was held for 2 s to assure intrapulmonary pressure equilibration. Pulmonary pressures obtained were plotted against inflation volume to construct pressure–volume curves of the lungs above FRC.

Forced Expiratory Volumes

Following the compliance measurements, the rabbits were placed into a sealed Plexiglas box for measurement of forced expiratory flows. The sealed Plexiglas box was pressurized to 25 cm H_2O.

Volumes of 60 cm^3 above functional residual capacity (FRC) were injected in the airway with a volumetric syringe. The syringe was disconnected from the endotracheal tube, and expiratory airflow through the pneumotach measured as volume was expelled from the lung. This expiratory maneuver was repeated four times for each rabbit examination. In order to determine the effective expiratory reserve volume, the pneumotach was left in place and the rabbit was disconnected from the ventilator. The box was again pressurized four times to 25 cm H_2O, then allowed to return to atmospheric pressure. The mean volume exhaled and inhaled was determined as effective expiratory reserve volume.

An analog-to-digital converter (Keithley system 570, Cleveland, OH) sampling at 60 Hz was used to digitize data, which were then stored on an IBM computer. Before measurements, the flow and pressure transducers were calibrated and zeroed against volumetric syringes and a water manometer, respectively. Flow was converted to volume by integration over time. Forced expiratory flows at 40 and 20 cm^3 inflation above FRC were calculated from the digital data. $FEV_{0.5}$ was also determined.

Flow measurements were made using a standard pediatric inline ventilator flow probe (Varflex flow transducer number 700-2-300, Bicor Monitoring Systems, Inc., Irvine, CA) connected to the endotracheal tube connector. The pressure from both sides of the flow transducer was recorded using a differential pressure transducer (Validyne, MP-45, Northridge, CA). The transducer output was connected to a carrier demodulator (Validyne Co., Northridge, CA), and the signal was sent to an analogue to digital converting board (Keithley system 570, Cleveland, OH) sampling at 60 Hz. For each pulmonary function maneuver, a calibrated 60-cm^3 breath was injected. Flow was recorded during injection and used to calibrate the system for measurement of the subsequent exhaled volume. Correction was made for conversion of ATPD to $BT_{(rabbit)}PS$.

Analog pressure measurements were obtained by placing a pressure transducer (Validyne, MP-45, Northridge, CA) probe in the respiratory tubing adjacent to the mouthpiece on the expiratory side, a standard 40-cm water manometer, or 60 cm H_2O pressure gauge. The transducer output was connected to a carrier demodulator (model MP 45, Validyne Co., Northridge, CA) and the signal was sent to an analog-to-digital converting board (Keithley system 570, Cleveland, OH) sampling at 60 Hz. The pressure transducer and gauge were calibrated with the water manometer prior to measurements.

All animals were fully anesthetized with relaxed chest walls during all measurements and were monitored continuously for respiratory activity by airway pressure and flow activity.

Thoracotomy

Anesthesia was induced in the rabbits with 2:1 ketamine HCl (100 mg/ml):xylazine (20 mg/ml) at a dose of 0.75 cm^3/kg im. Animals were intubated with a 3.0–3.5-mm cuffed pediatric endotracheal tube under direct laryngoscopic visualization using a number 1 straight-blade laryngoscope. Oxygen saturation (Ohmeda Biox 3700 Pulse Oximeter, BOC Health Care), end tidal CO_2 (Ohmeda 5200 CO_2 monitor, BOC Health Care), and electrocardiograph (EKG, Hewlett Packard 78353B continuous EKG temperature probe monitor, BioMedical Services) were monitored continuously. Rabbits were shaved, placed on a left lateral position, sterilely prepped with Nolvasan scrub, draped, and placed on ventilatory support (Harvard ventilator).

Operative Procedure

Thoracotomies were performed by strictly sterile surgical procedures. An incision was made between the 5th and 6th intercostal space between the pectoralis and latissimus dorsi muscles approximately 3–4 cm in length. Full anatomic examination was easily performed from this position.

Stapling

The lower lobe was isolated and mobilized into the incision after release of the inferior pulmonary ligament on its medial surface. Excision of 0.2–0.7 g of lung tissue was performed using Pediatric ENDO GIA staplers (3.5 mm × 30 mm, U.S. Surgical, Norwalk, CT). At the end of the procedure, a 12 French neonatal chest tube was placed to drainage.

Appropriate chest tube position was confirmed by direct inspection prior to closure. The tube was secured with 2–0 silk and attached to a Heimlich chest valve with suction (Gomco300, Allied HC, Baxter Hospital Supply, Irvine, CA). Closure of ribs was performed with 0 silk. Closure of subcutaneous tissue was performed with 3-0 Vicril or Dexon absorbable suture. Skin was closed with 4-0 Dexon subcuticular. If no air leak was seen following lung reexpansion, the chest tube was removed.

Control Groups

An additional 10 rabbits of the same species and age were divided into two different control groups. In the sham control group (5 rabbits), induction of elastase, measurement of pulmonary function, unilateral thoracotomy, and sacrifice were performed with identical methodology as for the study rabbits. The sham rabbits did not receive LVRS, but underwent thoracotomy. The lower lobe was isolated and the stapler placed over the lobe but not fired. The stapler was then removed and the thoracotomy closed analogous to the operative animals.

In the second control group, pulmonary function was measured in 5 normal rabbits at baseline, 4 weeks after baseline, and 5 weeks after baseline, at the time corresponding to the preoperative and presacrifice measurements in the other groups. These control animals did not undergo surgery or emphysema induction.

Statistics

Changes in compliance and flow curves among groups were assessed using analysis of variance (ANOVA) with repeatd measures with a standard statistical software package (Systat 5.1, SPSS, Inc.). Changes in flows from preoperative to postoperative within a group were compared using paired Student *t*-tests.

Histology

Animals were anesthetized as previously described, and 1000 U heparin was injected intravenously. Two cubic centimeters of Eutha-6 was administered IV and the descending aorta was severed for exsanguination. The lungs and heart were removed *en bloc*.

TABLE 1 LVRS emphysema model changes in compliance

	Volume above FRC (ml)				
Pressure (mm Hg)	*60*	*50*	*40*	*30*	*20*
Baseline	27.71	20.75	15.21	11.71	8.38
Preoperative	17.40	12.70	9.40	7.30	5.50
Postoperative	21.70	16.40	11.30	9.10	6.70
1 week Postoperative	17.55	12.15	8.75	7.05	5.15

Following necropsy, the lung was inflated by intratracheal instillation of 4% formaldehyde in phosphate-buffered solution at 25 cm water pressure for 24 h. Appropriate sections were processed routinely, embedded in paraffin, stained with hematoxylin and eosin (H&E), and studied by light microscopy. For this study, the degree of emphysema evident histologically was assessed subjectively under light microscopy by standard criteria of degeneration of alveolar septa, and enlargement of air spaces distal to terminal bronchi.

RESULTS

All animals survived the operative procedure until sacrifice at 1 week poststapling. The rabbits qualitatively had evidence of mild to moderate centrilobular or panacinar emphysema histologically (Figure 1). The distribution was microscopically focal but scattered diffusely throughout all lung fields.

Compliance

Baseline, preoperative, postoperative, and 1 week postoperative static respiratory system pressures were plotted against corresponding inflation volumes to construct respiratory system compliance curves (Table 1, Figure 2a).

Comparison of these compliance curves demonstrated a shift leftward from baseline to preoperative values ($p < .05$, ANOVA), suggesting an increase in static respiratory system compliance, as expected with induction of emphysema compared to baseline. Immediately postoperatively, the curve shifted to the right associated with a significant ($p < .05$) acute increase in static respiratory system pressures. However, by 1 week following surgery, respiratory system compliance curves returned to preoperative values (NS compared to preoperative).

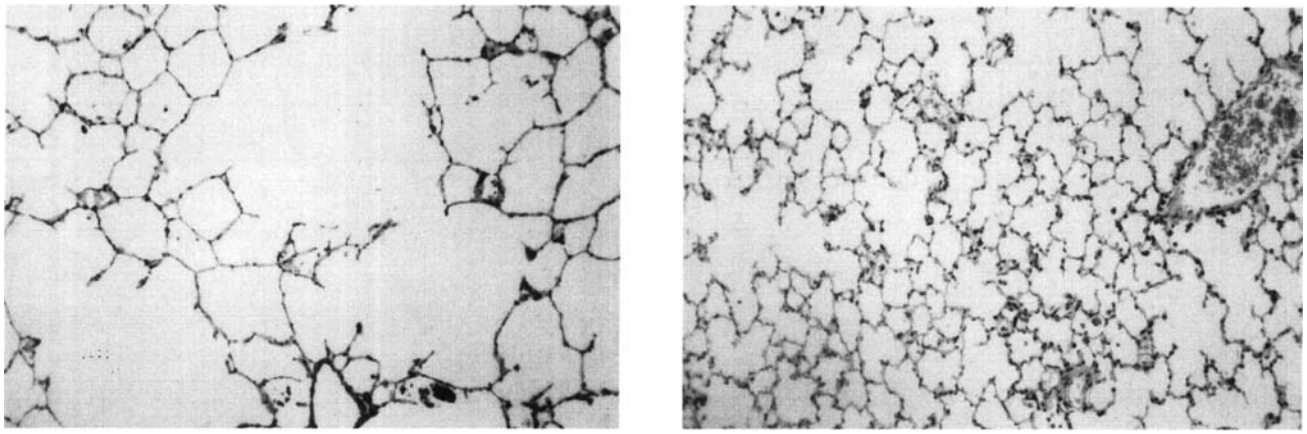

FIGURE 1 Histology of elastase-induced emphysema, showing histologic changes 4 weeks following elastase nebulization (left). Right image shows normal rabbit lung.

The inflation pressures of the sham and normal rabbits continued to decrease from baseline values to 5 weeks. This trend corresponds to a shift toward the left in the compliance curves, which suggests increased compliance (Figure 2, b and c).

Expiratory flows were plotted at 20 and 40 cc inflation above functional residual volumes (with 25 mm Hg externally applied pressure) (Figure 3). Flow–volume curves decreased following induction of bullous lung disease from 191 ml/s at 40 cm^3 above FRC to 132 ml/s ($p < .05$) and immediately following lung volume reduction surgery to 109 ml/s ($p < .05$). At 1 week postoperatively flow increased significantly ($p < .05$ compared to postoperative).

Maximal flow–recoil pressure graphs were constructed by combining the static pressure volume data with corresponding dynamic flow–volume data. Maximal flows were significantly higher at equivalent recoil pressures at baseline than after induction of emphysema ($p < 05$) (Figure 4). Immediately following LVRS, flows did not improve when adjusted for increased recoil pressures. However, by 1 week postsurgery, flows increased to nearly normal levels ($p < .05$), while recoil pressures decreased, implying increased respiratory system conductance (Figure 4).

DISCUSSION

We describe initial development of a heterogeneous emphysema animal model for investigating LVRS. We performed unilateral stapled lung volume reduction procedures, with static and dynamic pulmonary function measurements to determine the effects of volume reduction surgery on lung function in these animals.

Two major mechanisms have been proposed to account for increases in maximal expiratory flow following LVRS; increased elastic recoil, and increased tractional airway support [4–7]. By examining the relationship between static elastic recoil pressures and maximal expiratory flow, the relative contributions of these two mechanisms can be assessed [7]. We hypothesized that both lung elastic recoil and airway conductance would increase following LVRS in this model.

Maximal expiratory flow–static respiratory pressure curves were constructed by plotting dynamic maximum expiratory airflow (from the measured flow volume curves) against the static respiratory system pressure at each corresponding inflation volume above FRC (obtained from the static pressure–volume curves). Increases in respiratory system recoil are reflected in changes in the inflation pressure above FRC (though indirectly), while increases in airway support result in increases in maximal flow at equivalent recoil driving pressures.

Elastic recoil decreased and compliance increased as expected with induction of emphysema. Immediately following LVRS, increases in recoil pressure toward normal were seen in the rabbits. This parallels clinical reports of increased recoil pressure following LVRS in patients with severe emphysema [4–6,8]. However, by 1 week post LVRS, the recoil curves had returned to preoperative levels. The return

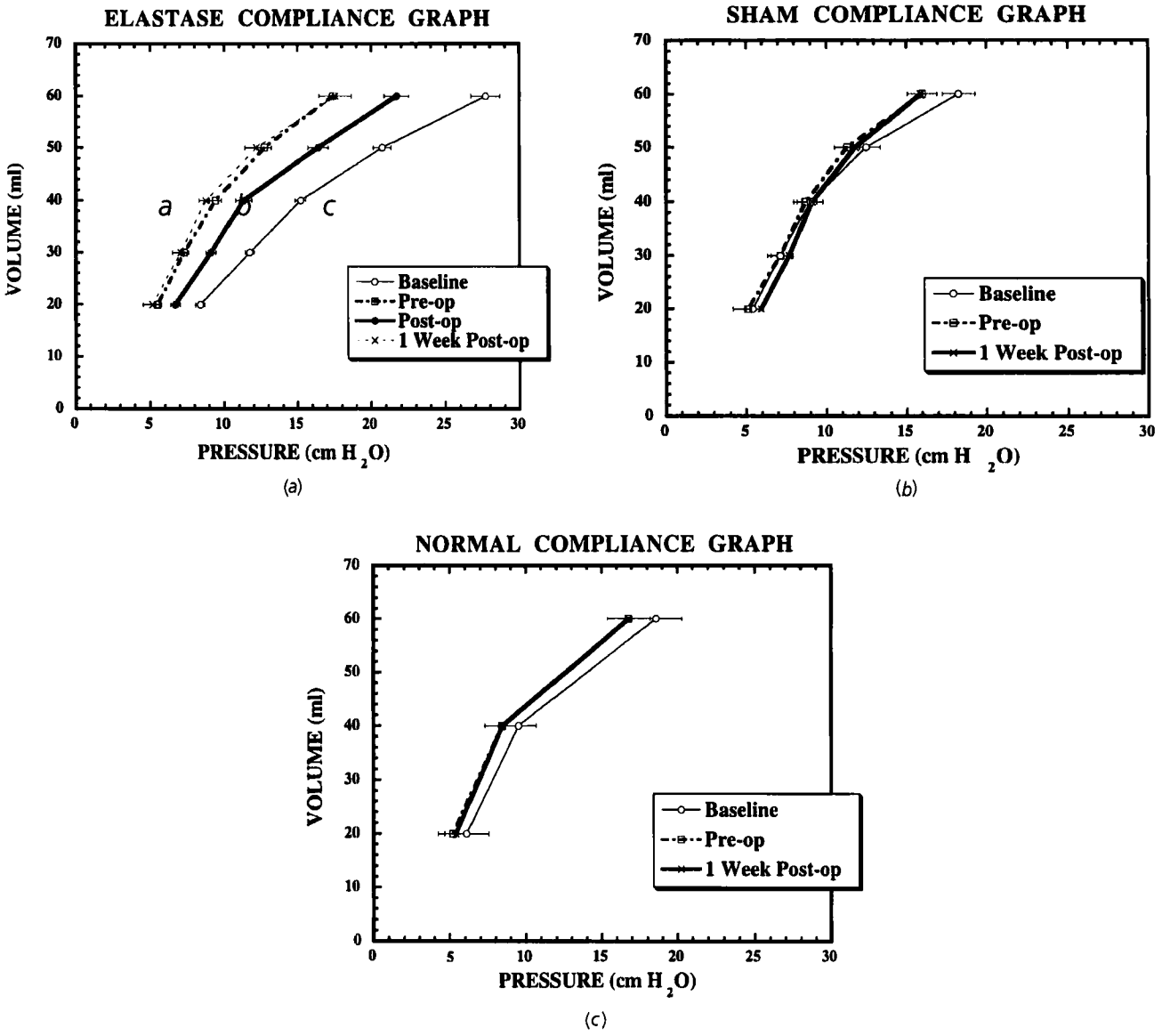

FIGURE 2 Compliance curves: (a) Elastase-treated animals. Graph shows static respiratory system compliance changes at baseline, preoperatively (4 weeks after induction of emphysema), immediately postoperatively following LVRS, and 1 week following surgery in elastase-treated animals. Standard error in pressure measurements are shown with Y-error bars. (*b*) Sham surgical controls. Graph shows static respiratory system compliance changes at baseline, preoperatively (4 weeks after induction of emphysema), immediately postoperatively following LVRS, and 1 week following surgery in elastase emphysema-induced, sham surgical control animals. (c) Normal animals. Graph shows static respiratory system compliance changes at baseline, at a time corresponding to preoperative (4 weeks after baseline), and 1 week later in normal rabbit controls.

toward preoperative levels probably reflects a number of factors, including resolution of acute postoperative edema and atelectasis, stress relaxation of lung tissue. Probable reduction in FRC following surgery was not accounted for in these studies since absolute lung volume measurements were not made. If reduction in FRC occurred as expected following LVRS, lung volume correction would likely reveal actual increases in volume adjusted recoil pressures.

In the sham-operated rabbits, the decrease in recoil pressure and increase in compliance seen at 1 week post sham surgery support a steady progression of the emphysematous disease process. Some increase in compliance seen in the normal controls may be attributed to animal growth.

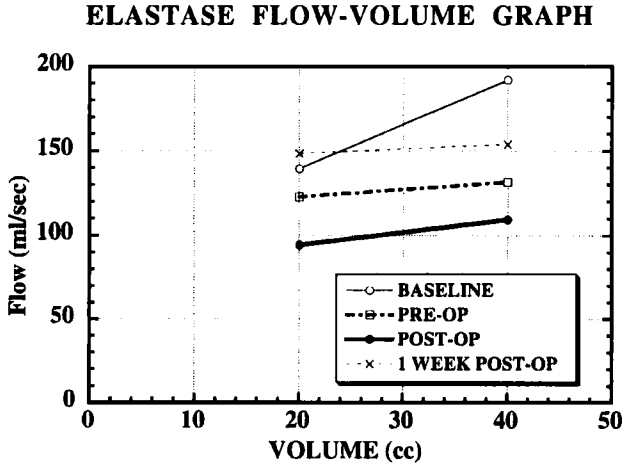

FIGURE 3 Flow–volume curves. Graph shows dynamic flow volume relationship at 33 and 66% of exhaled volume (40 and 20 cm^3, respectively) above FRC at baseline, preoperatively (4 weeks after induction of emphysema), immediately postoperatively following LVRS, and 1 week following surgery.

Expiratory flow rates increased in rabbits immediately postoperatively. However, flow rates were not increased when adjusted for the increased recoil driving pressure immediately post operatively. This most likely reflects acute increases in airway resistance in the immediate postoperative period. We conclude this because peak expiratory flows increased further by 1 week postoperatively, despite lower recoil driving pressures at that time. This suggests that the later

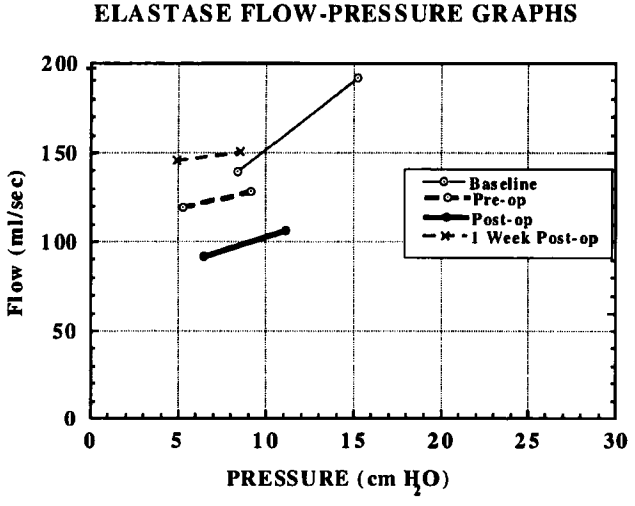

FIGURE 4 Flow–pressure curves. Graph shows dynamic flow–static recoil pressure relationship at 20 and 40 cm^3 above FRC at baseline, preoperatively (4 weeks after induction of emphysema), immediately postoperatively following LVRS, and 1 week following surgery.

effects of LVRS were due to reduced airway resistance and improved conductance in this unilateral LVRS rabbit model.

Under normal or restrictive lung disease conditions, one would expect conductance and recoil adjusted expiratory flows to decrease after removal of lung parenchyma due to removal of conducting airways. In obstructive lung disease, the loss of conducting airways is compensated for by the increase in airway support associated with reduction of the lung volume. Increased conductance in this model following LVRS provides physiologic evidence of clinically significant obstructive lung disease and supports the potential applicability of this model to investigate the effects surgical treatment of emphysema.

There are a number of limitations of this study. The methods employed assume that maximal expiratory flow has been achieved in order to determine airway conductance. In this apparently obstructive emphysema model, maximal expiratory flow appears to be achieved as evidenced by minimal differences between flows when the external pressurized box is inflated to 25 cm H_2O, compared to 20 cm H_2O.

Total lung volumes were not measured in these animals. All lung volumes are reported as volumes above FRC. Thus, changes in respiratory system compliance and flows above FRC seen in these animals may be affected by changes in the lung volume at which they were measures. However, lower lung volumes (i.e., lower FRC and TLC) following LVRS should be associated with decreased flows and conductance. Yet, flows and conductance increased after surgery, similar to findings in patients undergoing LVRS. Thus, even larger beneficial conductance effects of the procedure may have been obscured by reduction in lung volumes. Plethysmographic or gas dilution correction for absolute lung volume (with calculation of specific conductance, Sg_{aw}) will need to be performed in future studies to correct for the effects absolute lung volume.

The rabbits in this study were treated with unilateral lower lobe LVRS, with a relatively small amount of lung tissue removed. Little change in compliance was seen 1 week post LVRS despite the improved flows. In humans, improved recoil and conductance

may be seen following LVRS, which is most commonly performed bilaterally with predominantly upper lobe resection [4–6]. However, rabbits in this series did have involvement of the lower lobes with emphysema, rabbits are not upright animals like humans, and rabbit upper lobes are extremely small. Therefore, the most analogous lobe to resect in rabbits is not clear. Other factors that may have contributed to a lack of detectable compliance changes at 1 week following surgery include (1) the volume of lung tissue removed may be insufficient to cause substantial compliance changes, (2) lower lobe LVRS may not cause the same degree of response to LVRS as upper lobe removal, and (3) the compliant rabbit chest wall [9] may accommodate large changes in volume without significant changes in recoil pressure at FRC. Future studies employing larger volume bilateral upper lobe resections via median sternotomy, with concurrent absolute lung volume measurements, should be able answer these questions using this model system.

Lung compliance was assumed to closely parallel total respiratory system compliance (lung + chest wall compliance) in this study. Transpulmonary pressure measurements via esophageal balloon, required to determine static lung compliance, were not performed. The chest wall of the rabbit is extremely compliant and contributes very little to the measured respiratory system compliance from FRC to TLC. More importantly, changes in chest wall pressure preoperatively to postoperatively (the major measure of interest) at FRC and TLC following LVRS or sham surgery are very small given these wall compliance characteristics. Thus, failure to differentiate chest respiratory system from lung compliance changes in the rabbit does not appear to be as important as is in humans (in fact, this may represent one of the limitations of applicability of the rabbit model to humans).

We did not attempt to characterize the amount of lung resected beyond gross weight, nor did we attempt to normalize against the remaining lung volume in these studies. While this may limit interpretation of results, defining the amount of lung removed during resection remains an elusive problem. In humans, resected lung volume is grossly estimated at 20% of total lung volume. However, there is little objective basis for this estimation. Lung weight can be measured, but excised lung contains staples and variable degrees of denser bronchial tissues and vessels, and correlates very poorly with lung volume (especially in very emphysematous tissue regions). Resected lung volume measured by immersion has little correlation with the volume of tissue resected due to deflation and crushing. The difference between total lung volume before surgery and remaining lung volume after surgery does not accurately reflect the volume removed, due to compensatory changes in the remaining lung. Measuring the weight of lung resected as a function of weight of remaining lung also contains significant errors due to changes in fluid content that may occur between resection and later sacrifice, as well as the more important effects of associated bronchial and vascular tissue weights. Since all animals are single-species male New Zealand White rabbits of comparable age and weight, their baseline uniformity is some justification for using excised weight alone. Future studies with models such as this may better define methods for quantifying lung tissue removal.

The degree of absolute obstruction in this model is mild. Histologically and physiologically, patients undergoing LVRS have had more severe emphysema. Physiologic mechanisms of response may be different as severity of emphysema increases. Future studies using higher doses of repeated nebulizations of elastase may lead to a more severely emphysematous model. In current LVRS procedures, attempts are made to direct resection toward regions of lung with most severe emphysematous degeneration. It was not possible to direct the resection at specific areas of severe emphysematous degeneration in this animal model, since such regions were not macroscopically visible in most cases. This model appears to more closely approximate more diffuse emphysema that is being actively studied in the National Institutes of Health clinical trial than the more heterogeneous distributions previously studied.

In conclusion, this animal model demonstrates the feasibility of lung volume reduction procedures and methodology for assessing mechanisms of improvement following LVRS. In this model,

reductions in expiratory resistance with improved airway support and conductance appear to lead to improved expiratory flows following LVRS. The increases in flow and conductance following LVRS in this animal model are analogous to those seen in humans with emphysema and contrast with the decreases seen in a mixed restrictive–obstructive model [10]. Further studies using this model should help answer questions concerning LVRS for treatment of emphysema. ■

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