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Effect of Lung Volume Reduction Surgery in a Rabbit Model of Bullous Lung Disease

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ABSTRACT Clinical use of staple lung volume reduction surgery (LVRS) has proliferated for treatment of emphysema despite limited data regarding efficacy or optimal techniques. Recent studies in animal models of obstructive lung disease describe the decrease in lung compliance and increase in airway support as mechanisms of an improvement in pulmonary functions analogous to human data. We describe contrasting results in an animal model of bullous lung disease with a mixed but predominantly restrictive pattern of lung disease. Mixed restrictive and bullous lung disease was induced in 17 New Zealand white rabbits with iv Sephadex beads and endotracheally instilled carrageenan. Unilateral stapled lung volume reduction surgery was performed at 5 weeks postinduction of emphysema on the right lower lobe by lateral thoracotomy using a pediatric stapler. Static trans-pleural pressures were measured at 60, 40, and 20 cm^3 inflation at preinduction (baseline), pre- and postoperatively, and 1 week postoperatively in anesthetized animals. Lungs were then harvested en bloc and examined histopathologically. The effects of volume reduction surgery on static lung compliance, lung conductance, and forced expiratory flows (FEF) were assessed. Five weeks after induction of lung disease, the animals had no significant change in static compliance and forced expiratory volume in 0.5 s ($FEV_{0.5}$) or lung conductance compared to baseline. Immediately following LVRS, the animals showed a significant decrease in static compliance, $FEV_{0.5}$, and conductance. One week postoperatively, compliance increased to approximately baseline levels along with a slight increase in FEFs and conductance toward preoperative levels. Histology examination revealed restrictive and bullous lung disease. Thus, we have demonstrated the feasibility of using an animal model for evaluation of volume reduction therapy for restrictive-obstructive lung disease. Physiologically, this model showed decrease conductance and decreased forced expiratory flows following lung volume reduction despite increased recoil. This is in contrast to increased conductance and flows seen in humans with severe emphysema following surgery and

suggests that current criteria excluding patients with a significant restrictive component to their lung disease from LVRS surgery may be justified.

Surgical treatment of emphysema has recently gained wide clinical use due to advancements in surgical techniques of lung volume reduction [1,2]. However, the mechanisms of lung function improvement are still under investigation, and overall benefits of lung volume reduction surgery (LVRS) remain controversial.

In 1959, Brantigan et al. described the first clinical use of lung volume reduction for the treatment of diffuse emphysema [3]. The improvements in lung function were variable following this procedure, and volume reduction surgery did not gain favor. While there has been a revival of interest in LVRS in recent years [4–12], unresolved issues remain concerning preoperative factors associated with optimal outcome. Over 2,000 patients have undergone lung volume reduction surgery over the past 3 years [4–12], yet questions persist regarding outcome, patient selection, operative techniques, and mechanisms of response. Results of clinical LVRS operations have not been uniformly successful. Varying degrees of improvements suggest that the pathophysiology in emphysema is multifactorial. One of the main goals of preoperative selection criteria is to identify patients that will benefit from LVRS. It is hoped that improved selection criteria will assure more uniform lung function improvement [1,2,13].

Because definitive clinical data are currently lacking, we have developed animal models in an attempt to address some of these fundamental questions. We have concurrently developed two lung disease lung models. One model is of histologically pure obstructive pulmonary disease produced by nebulized elastase in New Zealand White rabbits. These animals were successfully treated by surgical lung volume reduction [14]. Findings in that purely obstructive rabbit model of emphysema suggest that pulmonary compliance is decreased while airway conductance and airway support are increased following LVRS, analogous to findings in clinical human studies [15].

We now describe development of a contrasting animal model of bullous lung disease that presents with histologically predominantly restrictive disease. There are no clinical data available for LVRS in patients with mixed obstructive-restrictive disease, and such patients are generally excluded from LVRS on theoretical grounds. We used this animal model to assess the response to LVRS in mixed obstructive restrictive disease.

We hypothesized that lung compliance would decrease in response to lung volume reduction as in the parallel purely obstructive animal model. However, one would predict less than optimal improvements in airflow and airway support compared to purely emphysematous disease.

METHODS

A total of 17 male New Zealand White rabbits (3 months old, 3–3.5 kg) underwent bullous emphysema induction using intratracheal carrageenan (10 cm^3, 0.7% solution) and intravenous Sephadex beads (0.3 cm^3 of 1 g/100 cm^3 suspension), according to previously published methods [16,17]. Pulmonary function studies were performed preinduction (baseline), immediately pre- and postoperatively, and again 1 week postoperatively. Pulmonary function testing was performed while the rabbits were intubated (3.0 mm, cuffed, endotracheal tube) under general anesthesia.

We examined static lung compliance, elastic recoil, and maximal expiratory flow-volume curves to determine airway resistance and conductance. This enables differentiation of the components of improved elastic recoil from increased airway support following surgery in this animal model [18,19].

Pulmonary Function Testing

Apnea was maintained with intravenous injections of 1:1 Ketamine/Xylazine and assessed with intraesophageal and airway pressure monitoring. Esophageal pressure was obtained by passing an esophageal balloon pressure catheter into the distal one-third of the esophagus. The balloon was gently inflated and the catheter position adjusted until a thoracic pressure tracing was obtained. Airway pressure was

obtained from the CO_2 port on the endotracheal tube. Transpleural pressure was calculated from recorded pressures. In addition, direct intrapleural pressure measurements were obtained from the chest tubes in rabbits as they underwent surgery to confirm accuracy of the esophageal balloon tracings.

Esophageal Pressure and Pleural Pressure Measurements

Static esophageal pressures were measured using an esophageal balloon system constructed in our laboratory with 1-mm-diameter silastic tubing with a 1-cm balloon sealed at the distal end and checked for leaks. With the animals under general anesthesia but breathing spontaneously, the balloon was passed orally until positioned in the stomach (positive inflection with inspiration). The balloon pressure was monitored by a water manometer via air-filled tubing. The balloon was withdrawn until 2 cm above the diaphragm by water manometer reading. The balloon was then deflated completely and reinflated with $\frac{1}{4}$ to $\frac{1}{2}$ cm^3 air under continuous pressure monitoring to avoid overinflation. The position of the catheter was marked and the catheter taped in position. Animals were then fully anesthetized until spontaneous respiration ceased for measurements. Pressures were recorded at functional residual capacity (FRC) and total lung capacity (TLC).

Pleural pressures were measured from the pleural chest tubes following surgery and compared to the pressures obtained via the esophageal balloon. Following reexpansion of the lungs with the chest tube to suction, 3–5 cm^3 of saline was injected into the chest tube if no air leaks were present. The chest tube was clamped then connected to the water manometer. The tube was unclamped and pressures were recorded at static levels of FRC and TLC.

Static Lung Compliance Measurements

Static lung compliance pressures were measured at inflation volumes of 60, 40, and 20 cm^3 above FRC. For these measurements, rabbits were taken off the ventilator. A volumetric calibrating syringe was attached to the end of the endotracheal tube, and the lung was hyperinflated to 60 cm^3 above FRC in order to standardize preinflation volumes. The lungs were allowed to passively deflate. The appropriate volume was injected; the syringe was held in place for 5 s and then released. This maneuver was repeated three times for each volume. The rabbits were returned to mechanical ventilation between trials.

Dynamic Expiratory Flow Measurement

Following the compliance measurements, rabbits were placed into a sealed Plexiglas box for measurement of forced expiratory flows. The rabbits were ventilated by means of external connectors while in the box. Flow was measured using a pneumotach and flow transducer connected to the end of the endotracheal tube. The box was pressurized and maintained at 20 cm H_2O pressure. Volumes of 60 cm^3 above FRC were injected in the airway with a volumetric calibrating syringe. The syringe was disconnected from the endotracheal tube, and expiratory airflow through the pneumotach was 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 20 cm H_2O, then allowed to return to atmospheric pressure. The mean volume exhaled and inhaled was determined as effective expiratory reserve volume. All flows and volumes were corrected to standard BTPS units.

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 volumes (FEVs) at 40 and 20 cm^3 inflation above FRC are calculated from the digital data. FEV in 0.5 s ($FEV_{0.5}$) was also determined.

Statistical Analysis

Changes in compliance and flow curves among groups were assessed using analysis of variance

(ANOVA) with repeated measures with a standard statistical software package (Systat 5.1, SPSS, Inc.). Changes in flows preoperative to postoperative within a group were compared using paired Student's *t*-tests.

Thoracoscopy

Thoracoscopy was performed 5–8 weeks after induction of emphysematous bullae. Anesthesia was induced with 2:1 Ketamine HCl (100 mg/ml): Xylazine (20 mg/ml) at a dose of 0.75 cm^3/kg im, and maintained with 1:1 Ketamine HCl (100 mg/ml): Xylazine (20 mg/ml) at bolus dosing to maintain apnea. The animals were intubated with a 3.0-mm cuffed endotracheal tube. Oxygen saturation (Ohmeda Biox 3700 pulse oximeter, BOC Health Care), end tidal CO_2 (Ohmeda 5200 CO_2 monitor, BOC Health Care), and EKG (Hewlett Packard 78353B continuous EKG temperature probe monitor, BioMedical Services) were monitored continuously. Rabbits were shaved and placed in the left lateral decubitus position, sterilely prepped with Nolvasan, alcohol, and Betadine, and draped. A Harvard ventilator (Harvard Apparatus dual phase control respiratory pump-canine, Harvard Co., South Natic, MA) was used for ventilatory support. Hypothermia was prevented with a surgical warming pad, and a 22-gauge iv catheter was placed in a marginal ear vein for infusion of lactated Ringer's solution at 5–15 cm^3/h.

Under sterile conditions, the lung surface was examined for evidence of bullae through two small 5-mm thoracoscopy trocars placed intercostally for full visualization. A 2- to 4-cm incision was made in the 7th intercostal space to allow the Multifire Endo GIA pediatric stapler (United States Surgical Corp., Norwalk, CT) access to the right lower lobe. The stapler was fired once across the periphery of the right lower lobe with excision of lung tissue with a mean weight of 0.5 g. A 12 French neonatal chest tube was placed under direct visualization into the pleural space, connected to suction (10 cm H_2O), and the wound was closed.

Repeat pulmonary function tests were repeated immediately postoperatively as well as 1 week postoperatively. At sacrifice the lungs were removed en bloc and inflated with formalin (20 cm pressure) for histologic preparation.

Control Group

An additional five New Zealand White rabbits of similar size and age comprised the sham control group. Induction of bullous lung disease, measurement of pulmonary function, and visual thoracoscopy were carried out in the exact manner as the study group; however, these rabbits did not receive LVRS.

Histologic Preparation

The lung sections were prepared at 0.2 to 0.4 cm thickness and embedded in paraffin. Slides were stained with hematoxylin–eosin and studied by light microscopy. Coded histopathologic specimens were reviewed by a pathologist blinded to clinical data.

RESULTS

All animals survived the procedure until sacrifice at 1 week poststapling. All rabbits had a mixed histologic presentation of bullous changes, inflammatory reaction, and fibrotic reaction to the carrageenan and Sephadex beads seen at the time of sacrifice as compared to normal rabbit lungs (Figure 1).

At 60, 40, and 20 cm^3 inflation above functional residual capacity (FRC), average baseline pressures (prior to induction) were 19 ± 0.6 (SEM), 11 ± 0.4 (SEM), and 6 ± 0.7 (SEM) cm H_2O, respectively (Table 1). Average preoperative pressures were 19 ± 0.5 (SEM), 10 ± 0.4 (SEM), and 6 ± 0.4 (SEM) cm H_2O. Average postoperative pressures were 21 ± 0.6 (SEM), 12 ± 0.5 (SEM), and 7 ± 0.7 (SEM) cm H_2O. Average 1 week postoperative pressures were 18 ± 0.8 (SEM), 11 ± 0.6 (SEM), and 6 ± 0.3 (SEM) cm H_2O (Table 1).

Baseline, preoperative, postoperative, and 1 week postoperative transpleural recoil pressures were plotted against corresponding inflation volumes to construct lung compliance curves (Figure 2). Comparison of these compliance curves demonstrated minimal shift leftward from baseline to preoperative. Postoperatively, the curve shifted significantly to

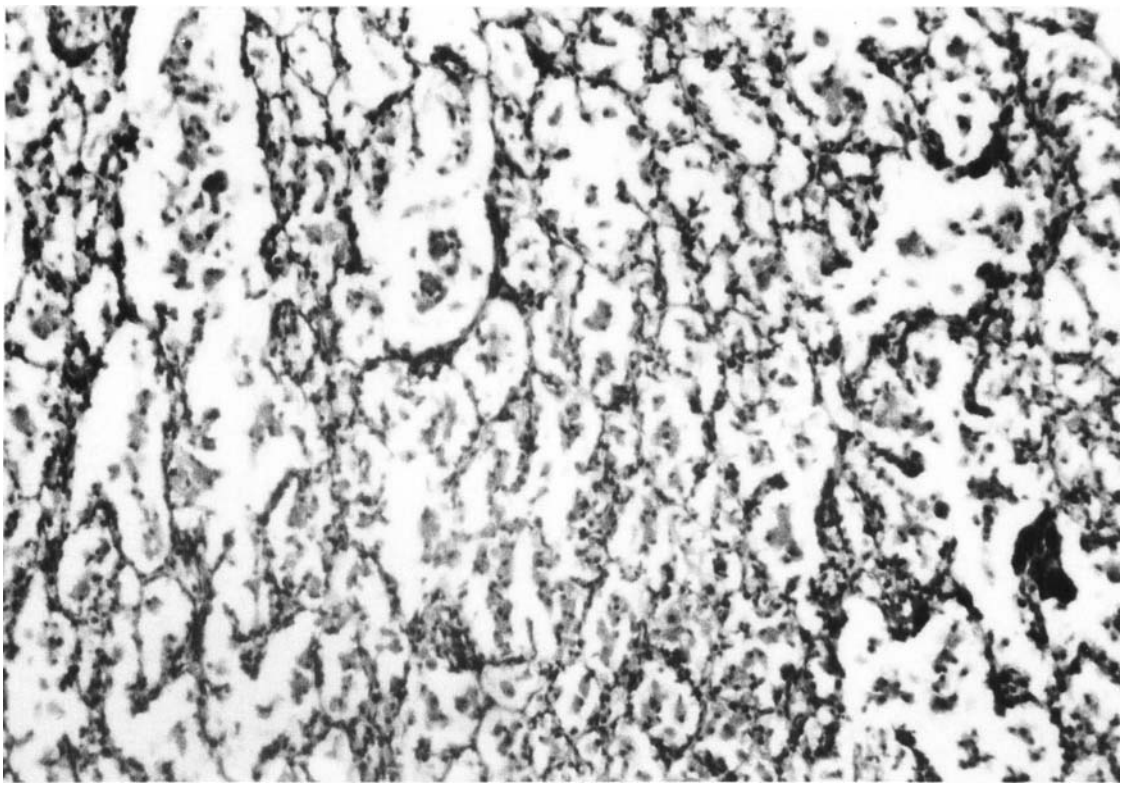

FIGURE 1 Histologic changes 4 weeks following carrageenan induction of emphysema. Magnification 10×. Hematoxylin–eosin stain.

the right, past baseline values ($p < .05$ compared to preoperative baseline ANOVA). This corresponds to a significant increase in static transpleural pressures with a corresponding decrease in static compliance. However, within 1 week following surgery, lung pressures decreased to nearly baseline values ($p =$ ns).

The compliance curves of the sham group showed no significant change from baseline to preoperative or following sham surgery ($n = 5, p =$ ns).

Forced expiratory flows were plotted at 20 and 40 cm^3 inflation above functional residual volumes. The average $FEV_{20\,cm^3}$ and $FEV_{40\,cm^3}$ at baseline were 118 and 152 mL/s; at preoperative, 112 and 147 mL/s; at postoperative, 88 and 140 mL/s; and at 1 week postoperative, 89 and 149 mL/s. Flow–volume curves decreased following induction of bullous lung disease ($p < .05$ by paired t-test compared to baseline) and did not increase following staple lung reduction surgery or at 1 week postoperatively ($p =$ ns) (Table 1).

Maximal flow–recoil pressure graphs were constructed by combining the static pressure volume with corresponding dynamic flow–volume graphs (Figures 2 and 3). The slope of the maximal flow–pressure line corresponds to airway conductance and indicates airway support [18]. Preoperative airway conductance was 2.15 mL/s/cm H_2O and remained

TABLE 1 Average pressures at varied inflation after carrageenan induction of bullous emphysema

	Baseline	*Preop.*	*Postop.*	*1 Week postop.*	*p (preop–postop)*
Average pressure at 20 cm^3 (cm H_2O)	6.24	6.2	7.03	6.3	NS
Average pressure at 40 cm^3 (cm H_2O)	11.0	10.2	11.8	10.7	0.004
Average pressure at 60 cm^3 (cm H_2O)	18.9	19.0	21.4	18.5	0.0002
Airway conductance (mL/s/cm H_2O)	1.85	2.15	1.85	2.0	NS

Note: NS, not significant.

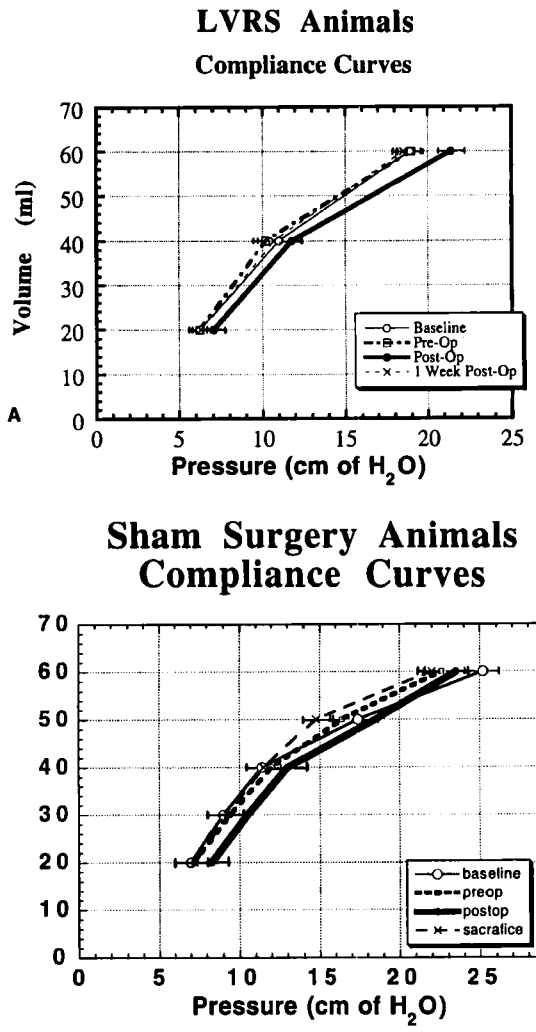

FIGURE 2 Static lung compliance changes at baseline, preoperatively (4 weeks after induction of emphysema), immediately postoperatively following LVRS, and 1 week following surgery. (A) Staple LVRS. (B) Sham LVRS.

unchanged postoperatively. Of note from Figure 4, maximal flow–pressure graphs revealed a slightly decreased flow despite increased elastic recoil pressure with no significant change in slope. These findings suggest that no improvement in airway conductance occurred, despite increased recoil pressures postoperatively.

Again, the sham group followed a trend similar to the study group. Expiratory flows dropped from baseline to preoperative. Immediately postoperatively, there was a slight increase in expiratory flows. However, this improvement was short-lived, as flows dropped below baseline values at 1 week postoperatively (Figure 4).

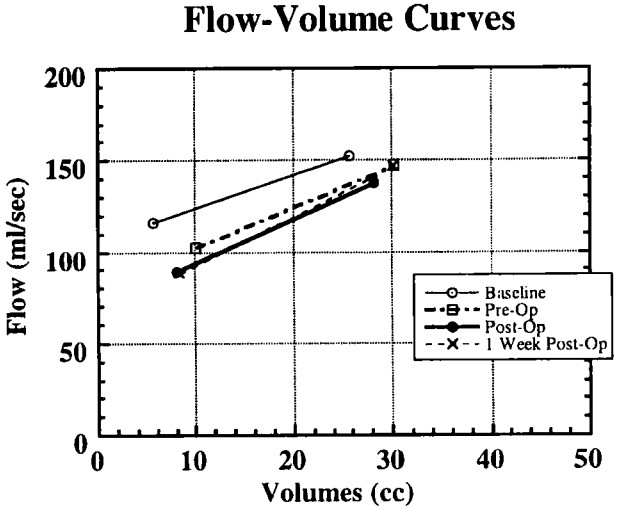

FIGURE 3 Dynamic flow–volume relationship at 33 and 66% of exhaled volume (40 and 20 cm^3, respectively) at baseline, preoperatively (4 weeks after induction of emphysema), immediately postoperatively following LVRS, and 1 week following surgery.

DISCUSSION

There are several important points elucidated by this model. First, investigations in LVRS can be accomplished in a rabbit model of emphysema. Pulmonary function testing and surgical volume reduction can be performed safely and reproducibly in rabbits. Second, although lung compliance decreases in response to volume reduction, this is not

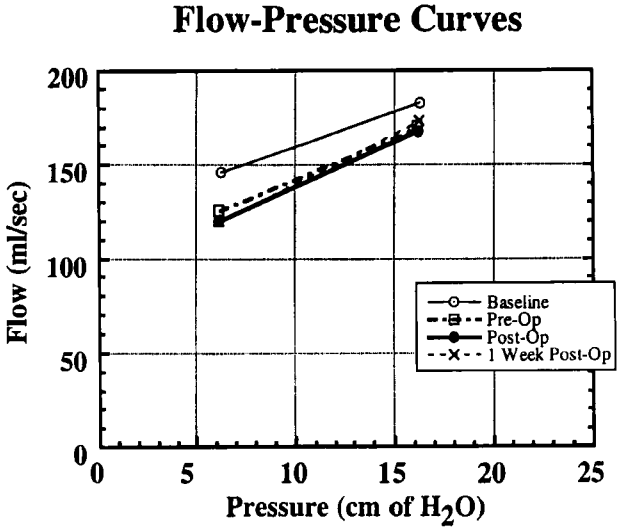

FIGURE 4 Dynamic flow–static recoil pressure relationship at 20 and 40 cm^3 above FRC at baseline, preoperatively (4 weeks after induction of emphysema), immediately postoperatively following LVRS, and 1 week following surgery.

necessarily associated with improvements in flow and airway conductance, as seen in this mixed restrictive pulmonary disease model. Extrapolating this experience to the clinical practice of LVRS in the setting of mixed obstructive-restrictive pulmonary disease, LVRS may not provide the physiologic benefits seen in a purely obstructive disease.

In order to investigate mechanisms of airflow limitation pre- and postoperatively, we evaluated the driving pressure for expiratory airflow (elastic recoil) and airway conductance. We found increased recoil pressure but decreased airway conductance immediately following stapling. This contrasts with results of LVRS in clinical studies as well as those of our other animal models of pure obstructive emphysema [14,15]. Increases in both recoil pressure and conductance were found following LVRS in the setting of isolated obstructive disease.

While lung elastic recoil increased in the mixed obstructive restrictive rabbits in the current study, flow rates did not increase. In fact, flows tended to decrease when adjusted to equivalent lung recoil pressures. This suggests that the major effect of LVRS was increased lung elastic recoil. There is no evidence for improved airway support or airway conductance under these conditions.

In the sham-operated rabbits, we found decreased recoil pressure and progressively decreasing flows. The fact that the results of our control group seem to follow the same trend as our study group further suggests the surgery was of little benefit to our study group.

There are a number of possible causes for the decreased airway conductance response to lung volume reduction surgery seen in this animal model in contrast to emphysematous humans. Histologic analysis revealed that carrageenan and Sephadex beads induced mixed obstructive-restrictive changes in this rabbit model, with predominantly restrictive appearance. In addition to bullae, the rabbit lungs showed evidence of inflammation and scarring [20]. The presence of this restrictive component appeared to determine the outcome of LVRS. When lung tissue is removed in restrictive disease, the recoil adjusted expiratory flow decreases due to removal of functional conducting airways. In this mixed obstructive-restrictive model, there would have to be a proportionally greater increase in caliber and support of the remaining conducting airways as compared to the amount of functional conducting tissue removed or overall conductance would decrease. This contrasts with a pure emphysema model, where the resulting increase in airway caliber of poorly supported airways would likely exceed the reduction due to removal of airways.

Second, endotracheal tube resistance may impair our ability to detect changes in airway conductance in a mixed restrictive model. The number 3 endotracheal tube has substantial resistance, which is in series with the conducting airways. If endotracheal resistance is too high in relation to the native airways, flow limitation would shift to the endotracheal tube site, and changes in airway support caliber may be undetectable. Additionally, maximal expiratory flows may not have been reached at 20 cm H_2O of externally applied pressure in the body box. The methods employed in this study assume that maximal expiratory flow has been achieved in order to determine the degree to which expiratory airway support affects conductance [18]. Nevertheless, results under these same conditions in a purely obstructive lungs model of severe emphysema revealed different responses with increased flows and conductance postoperatively [14].

Clinical experience in humans suggested that patients with lower lobe disease do not generally respond as well to LVRS or bullectomy as patients with upper lobe disease [9,20]. The reasons for this are not understood at this time. In a similar fashion, lower lobe volume reduction in our animal model may have provided suboptimal improvements in airway conductance and obscured the beneficial effects of volume reduction. Further investigation is needed to clearly identify the physiologic basis for this difference in improvement.

The LVRS procedures in this study were unilateral lower lobe resections. In humans, most current approaches involve bilateral upper lobe resections via median sternotomy or bilateral Video Assisted Thoracoscopic Surgery (VATS) procedures. Physiologic responses may be different if such approaches were used in the rabbits.

Total lung volumes were not measured in this model. Given the presence of mixed restrictive and obstructive disease, the absolute lung volumes may have increased, decreased, or remained unchanged with induction of bullous lung disease. Future studies may be performed with this model with measurements of absolute lung volumes. Regardless of the resultant lung volumes, recoil-adjusted flows decreased following LVRS, which contrasts with findings in models of pure emphysema. These findings suggest that current caution appears justified in excluding patients with significant components of mixed obstructive-restrictive disease from LVRS. ■

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