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Authors
Brenner, Matthew
Gonzalez, Xavier
Jones, Blanding
et al.

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Effects of a Novel Implantable Elastomer Device for Lung Volume Reduction Surgery in a Rabbit Model of Elastase-Induced Emphysema*

Matthew Brenner, MD, FCCP; Xavier Gonzalez, MD; Blanding Jones, MD;
Rick Ha, BS; Kathryn Osann, PhD; Robert McKenna, MD; and
Jeffrey Milliken, MD

Objectives: There is intense interest in lung volume reduction surgery (LVRS) for treatment of severe symptomatic emphysema. LVRS results in objective and subjective improvement in lung function in selected patients. However, LVRS is complicated by substantial morbidity, including prolonged pulmonary air leak associated with resection of emphysematous lung tissue. In this study, we investigated the use of a novel implanted silicone elastomer device that reduces lung volume without surgical resection, in a previously reported emphysematous animal model. The purpose of this investigation was to determine the applicability, physiologic effects, complications, and air-leak results of this lung volume reducer (LVR) approach.
Design: Controlled, randomized, prospective animal study. Emphysema was induced in 20 New Zealand white rabbits with three nebulizations of 10,000 U of porcine elastase. After 6 weeks, the animals were randomized to control sham surgery (n = 10) vs implanted silicone elastomer LVR (n = 10) treatment groups. Lung function, including helium-dilution lung volumes, static respiratory system compliance curves, and diffusion capacity of the lung for carbon monoxide (D_{LCO}), was measured at baseline, following emphysema induction (week 6), and when the animals were killed (1 week after LVR or sham surgery). Histologic evaluation was performed in all lung specimens after fixation.
Results: Moderate emphysema developed after elastase nebulization, assessed by lung function and postmortem histology. Functional residual capacity (FRC) and an upward shift of lung compliance curves was observed with development of emphysema at 6 weeks (p < 0.05). Following LVR, FRC decreased (p = 0.005) and compliance curves shifted back downward (p = 0.002), without reduction in D_{LCO}. There was no change in control sham animals. D_{LCO} did not change in either group.
Conclusions: In this short-term, randomized, controlled animal model study, the implantable LVR approach produced safe and effective lung volume reduction without tissue resection in the treated animals. The implant procedure produced minimal morbidity, no mortality, and no observed air-leak complications in the treated animals. Limitations include the short-term follow-up and moderate degree of emphysema in this animal model. Further research is required to assess long-term effects and complications of this method for lung volume reduction.
(CHEST 2002; 121:201–209)

Key words: air leak; lung volume reducer; lung volume reduction surgery; silicon

Abbreviations: ANOVA = analysis of variance; D_{LCO} = diffusion capacity of the lung for carbon monoxide; FRC = functional residual capacity; LVR = lung volume reducer; LVRS = lung volume reduction surgery

Emphysema is a progressive pulmonary disease characterized by abnormal and permanent enlargement of airspaces distal to the terminal bronchioles, accompanied by the destruction of their alveolar wall.[1] Symptoms include breathlessness and exercise limitation due in part to reductions in lung elastic recoil, airway support, and the surface area of

the alveolar-capillary bed. Approximately 14 million Americans have COPD, and at least 2 million Americans have predominantly emphysema.[2] The economic and social costs of emphysema is enormous, with quality-of-life and economic impact proportional to disease severity.[3]

Since 1993, there has been a resurgence of interest in lung volume reduction surgery (LVRS) for selected patients suffering from advanced emphysema.[4] By selectively removing portions of diseased lung tissue, LVRS restores some elastic recoil airway support properties within the lung.[4–11] Bilateral LVRS via either open median sternotomy or video-assisted thoracoscopy surgery has generally become the standard lung reduction treatment procedure for most patients in recent years.[4,12–17] In most cases, a linear surgical stapler is used, with multiple targeted excisions performed to remove the most severely affected regions of lung tissue. Bovine pericardial buttressing or other support is frequently used in an attempt to control air leakage.[4,18–20] The target lung is periodically inflated to evaluate the degree of reduction and the need of further resection. Multiple air leaks are frequently observed and may become more pronounced when the emphysematous tissue is torn by the tension of reinflation, when high levels of chest tube suction are needed, or when positive-pressure ventilation is required. Air leaks are the most common intraoperative and postoperative complication of LVRS and determinant of duration of hospitalization.[18,19,21–23] When minimal postoperative air leaks persist, patients may be discharged with Heimlich valves connected to chest tubes.[23,24] While the use of bovine pericardium and other biocompatible materials to reinforce the staple line has decreased the incidence and severity of air leaks, it has not eliminated this significant problem.[4,18–23]

We have developed a novel approach to accomplish lung volume reduction. This method involves implanting a very thin silicone elastomer device onto emphysematous segments of lung tissue, compressing them and preventing their reinflation (Fig 1, *left*, A). The system utilizes a vacuum force to draw the selected segment of lung tissue into the silicone device (Fig 1, *right*, B). Silicone is a biocompatible material that has been extensively implanted in humans, produces limited inflammatory response, and has enough elastic force to maintain the lung tissue in a collapsed state after implantation. The procedure is fast, and air leaks and bleeding appear to be prevented by tissue compression after device deployment.

A multiple elastase emphysema rabbit model was used to test the effectiveness of this lung volume reducer (LVR) device approach. In this model, a moderate degree of emphysema develops with histologically demonstrated alveolar wall destruction and concomitant changes in pulmonary function. A single elastase nebulization model has been extensively used in our laboratory to test the efficacy of standard LVRS, video-assisted thoracoscopy surgery, and laser techniques in previous investigations.[25–28] More extensive emphysematous changes were shown to result from multiple nebulizations.[29,30] In this study, 20 emphysematous animals were classified into two groups, an experimental arm (n = 10) implanted with the LVR device, compared to a control arm (n = 10) treated with sham surgery. The purpose of this investigation was to determine the feasibility, physiologic effects, complications, and air-leak results of this implantable LVR device approach in the emphysematous animals.

MATERIALS AND METHODS

A previously described rabbit model of emphysema was used.[29,30] All procedures in this study were performed under an approved animal research protocol (Institutional Animal Care and Use Committee No. 97–1556). All rabbits were cared for in accordance with National Institutes of Health guidelines for the care and use of laboratory animals.

Animal Preparation

New Zealand white rabbits (mean ± SD weight, 3.8 ± 0.25 kg) were used for these studies. For determinations of pulmonary
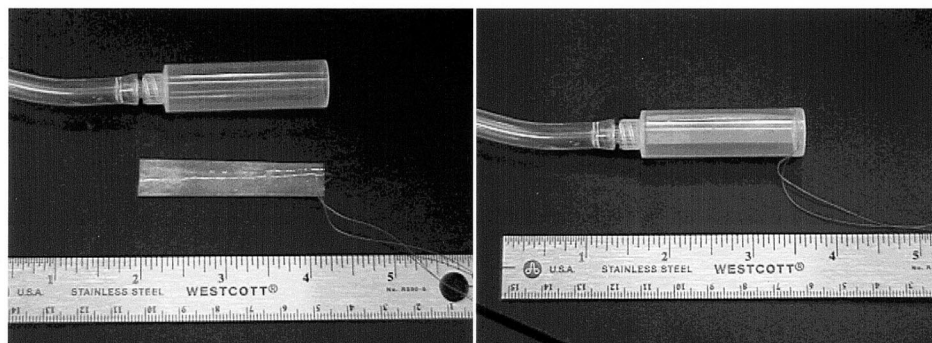

FIGURE 1. The LVR system: *Left*, A: LVR silicone device with purse-string suture and vacuum chamber. *Right*, B: LVR device inside the vacuum chamber.

function, elastase nebulization, surgeries, and final studies, all animals were anesthetized in the same manner. Rabbits were sedated with a 2:1 mixture of ketamine hydrochloride and xylazine administered IM and received mechanical ventilation (Harvard Apparatus Dual Phase Respiratory Control Pump; Harvard Apparatus; South Natick, MA). Anesthesia was maintained with 0.3-mL 1:1 mixture of ketamine and xylazine administered in IV boluses as needed to maintain apnea throughout all procedures. An indwelling catheter was placed in a marginal ear vein for fluid and anesthesia administration. During all procedures, the vital signs of the animals were continuously monitored.

Induction of Emphysema

Emphysema was induced in all rabbits by aerosolizing porcine pancreatic elastase (Worthington Biochemical Corporation; Lakewood, NJ) through the endotracheal tube. The nebulizer (Respirgard; Marquest Medical Products; Engelwood, CO) was placed in the inspiratory arm of the ventilator circuit. Nebulizations of 10,000 U of elastase were administered at week 1, week 2, and week 4, following a protocol that has been shown to produce moderately severe emphysema in this animal model.[29,30] Concomitant with elastase, an albuterol sulfate inhalation solution (0.03 mg/kg) was administered to improve aerosol deposition and to prevent bronchoconstriction. Two rabbits died during the elastase nebulizations; the cause of death was pneumothorax and pulmonary hemorrhage due to erosion from the elastase. A 20% mortality during induction of emphysema was expected in this model. The deceased animals were promptly replaced.

Pulmonary Function Testing

Lung function testing was performed at baseline before induction of emphysema (week 0), at week 6 immediately preoperatively (after induction of emphysema), and 1 week after the operation. Static lung compliance and gas dilution lung volumes were measured at each time interval (Fig 2).

Static Compliance

Static respiratory system compliance pressures were measured at inflation volumes of 60 mL, 50 mL, 40 mL, 30 mL, and 20 mL above functional residual capacity (FRC). For these measurements, the anesthetized rabbits were disconnected from the ventilator and placed in a left decubitus position. A volumetric calibrated syringe was attached to the end of the endotracheal tube. The lung was hyperinflated to 60 mL above FRC three times to standardize preinflation volumes, and then allowed to passively deflate. The appropriate compliance volume was then injected and the syringe held in place for 5 s, static pressures

were measured, and the syringe was released. This maneuver was repeated two times for each volume and pressures averaged.

Gas Dilution Lung Volumes

Helium-Dilution Lung Volume Measurement: Lung volumes were determined by multibreath gas-dilution methods in the anesthetized, intubated animals. The side port of the endotracheal tube was connected to a mass spectrometer that continually sampled the gas in the endotracheal tube in-line. The lung at FRC was inflated repeatedly and equilibrated with 60 mL of inhalation gases consisting of 9.30% helium, 60.5% oxygen, 29.05% nitrogen, 0.87% acetylene, and 0.28% C18O (Liquid Carbonic; Los Angeles, CA). All gas concentrations were measured by mass spectrometry (model MGA 1100; Perkin Elmer; Norwalk, CT; and Marquette; St. Louis, MO). The data were converted to digital information by an analog-to-digital converter (Keithley System 570; Keithley; Cleveland, OH) sampling at 20 Hz and stored on a personal computer. The initial and final helium concentrations were used to calculate the absolute lung volumes.

Carbon Monoxide Lung Diffusion Capacity Measurement: Diffusion capacity of the lung for carbon monoxide (DLCO) measurements were determined by the gas dilution method in anesthetized, intubated animals. The lung was inflated for 5 s to simulate a 5-s breath-hold DLCO. The lung was then deflated using a syringe. The initial and final helium and carbon monoxide gas concentrations were obtained at midexhalation (30-mL volume) as measured by the mass spectrometer. A computer program that analyzes the stored gas absorption data for single-breath, multibreath, and constant exhalation maneuvers was utilized. Individual gas absorption concentration time curves were plotted. All simultaneous volume and gas concentration curves were aligned in-time, correcting for instrumental dead space and sampling delays. Log gas concentrations were corrected by concurrent log helium reference gas concentrations. Lung volumes were determined by direct helium-dilution measurements. Anatomic dead space, determined by the Comroe-Fowler method during continuous volume withdrawal for each exhalation maneuver, was integrated over the time of the gas concentration plateau. DLCO was calculated after correction for temperature and humidity change from the 60-mL single-breath injection maneuver. Rebreathing lung volumes and helium-equilibration times were determined by extrapolating rebreathing best-fit decay curves until 99.95% helium equilibration occurred during 50-mL rebreathing maneuvers.

Surgical Procedure (Week 6)

After randomization to either the control (sham) or experimental (LVR implant) group, each animal was anesthetized with a
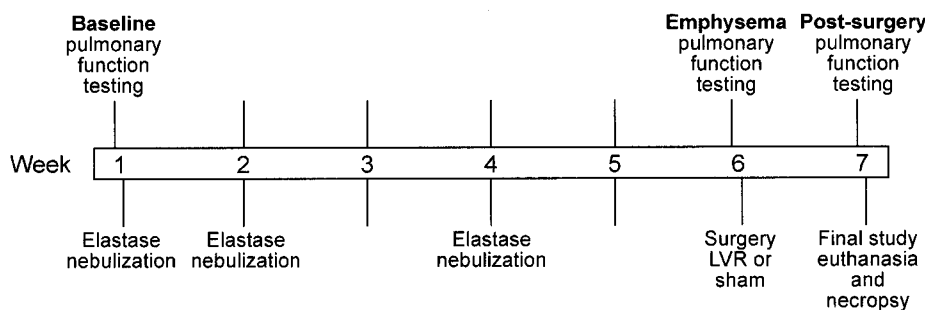

FIGURE 2. Study timeline in weeks showing the different testing and procedures performed in all animals.

combination of 3-mL 2:1 ketamine hydrochloride (100 mg/mL) xylazine (20 mg/mL) IM injection. All animals were administered prophylactic doses of antibiotic (enrofloxacin) and analgesic (butorphanol tartrate) IM at appropriate doses calculated by body weight. A 22-gauge catheter was place in the left marginal ear vein for IV access and administration of fluid during surgery. The animals were intubated with a 3.0-mm pediatric endotracheal tube and immediately connected to a Harvard ventilator set at 60-mL tidal volume and 35 to 45 breaths per minute. Bolus injections of 1:1 ketamine/xylazine were administered as needed to maintain anesthesia for the duration of the procedure.

Using standard surgical techniques, a median sternotomy was performed exposing the heart and the lungs. In the control group, after median sternotomy, the pleural membrane was opened exposing the lungs. Two chest tubes were placed, one in each hemithorax, and the incision was closed in planes. In the experimental group, the lungs were exposed in similar fashion, and the regions to be reduced were identified in the right upper lobe, right middle lobe, and left upper lobe. Based on previous morphometric studies done in this animal species, appropriate-size silicone devices were used. In each device, immediately before implantation, a purse-string suture (3–0 silk) was placed in one of the ends of the device to secure it in place once deployed. The devices were loaded inside a vacuum chamber (Fig 1, right, B), and the chamber was connected to a vacuum pump (Gomco model 400; Allied Healthcare Products [Gomco Division]; St. Louis, MO). The device and vacuum chamber are constructed with clear, transparent material allowing the operator to visualize and select emphysematous areas for reduction, and to visually assess the lung drawn into the device. Just before implant, the ventilator was stopped and the lungs were allowed to passively deflate for approximately 10 s. Using a vacuum force that did not exceed approximately 200 mm Hg, the targeted lung tissue was drawn into the device until the desired amount of tissue was captured, the vacuum was interrupted, and the device deployed. Each of the devices was implanted through the anterior aspect of the upper right lobe, middle right lobe, and upper left lobe, covering and compressing at least one third of the lobe volumes (Fig 3, left, A). After each device deployment, the device was fixed in place by pulling the purse-string suture and applying manual knots until the device was secured and the ventilator restarted. In some instances, when the position was not ideal and/or more tissue needed to be reduced, the reducing silicon elastomer device was removed and another device was placed over the lung tissue without complication. A U-stitch suture was placed in the distal portion of the device and the reduced lung tissue to secure it in place (Fig 3, middle, B, and right, C). After each implant, the lungs were reinflated and device location and fixation were evaluated. When all implants were completed, careful observations were made for air leaks by filling the thoracic cavity with warm 0.9% saline solution and looking for bubbles during ventilation. After the saline solution was removed, chest tubes were placed in each hemithorax as described for the sham group, and the incisions were closed in planes.

The chest tubes were connected to Heimlich valves, and the valves were connected to a vacuum water-trap system to evaluate air leaks. The water-trap system was evaluated by direct visual observation for 30 to 40 min, and the presence or absence of air leaks were documented. Per protocol, if air leaks were observed, the chest tubes were left in the rabbit until the air leaks resolved. If no air leaks were observed, the tubes were removed as the animal recovered from anesthesia. The rabbits remained on oxygen support until they maintained adequate oxygenation and ventilation on their own. When completely recovered, the animals were returned to animal housing. Daily observations and administration of analgesics and antibiotics were performed during the week following surgery.

### Final Study, Euthanasia, and Necropsy (Week 7)

One week after surgery, the animals were sedated and intubated. Lung function testing, including FRC, compliance curves, and DLCO, was repeated in all animals. The animals were then anesthetized and administered mechanical ventilation. The chest was reopened via median sternotomy, and the intrathoracic structures were exposed. Observations were made on tissue and implant conditions, adhesions, fibrosis, and presence of fluid in the thoracic cavity. If fluid was observed, it was carefully removed and measured with a syringe. When all observations were completed, each animal was killed with an IV injection of euthanasia solution (Euthasol; Delmarva Laboratories; Midlothian, VA). Heart and lungs were removed en bloc, the trachea was cannulated, and the lung tissue was infused with 10% formalin solution at 20-mL pressure for 24 h for tissue fixation.

Histology

Once fixated, the preserved lung tissue was separated from the heart, and examined and weighed. Representative sections of each lobe, including reduced and nonreduced areas, were obtained. The tissue from experimental and control animals was sectioned in approximately the same regions in slices of 0.2- to 0.4-cm thickness and embedded in paraffin. Slides were stained with hematoxylin-eosin using standard methods.

Histologic specimens from all lobes of experimental and control animals were reviewed by an independent American College of Veterinary Pathologists board-certified veterinary pathologist, blinded to clinical information. Lung tissues were compared for microscopic examination using routine histology techniques of paraffin embedding and hematoxylin-eosin stain-

FIGURE 3. Drawings showing the implant procedure of the LVR devices onto rabbit lungs. Left, A: Lung lobe region to be reduced is drawn into the LVR device using the vacuum chamber. Middle, B: Vacuum chamber is withdrawn, leaving LVR device encapsulating and compressing a selected region of lung lobe. Right, C: LVR device is secured with sutures at the distal and proximal ends.
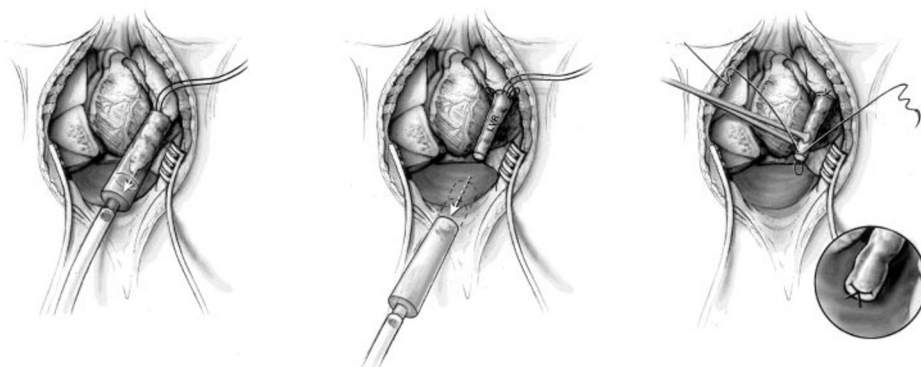
ing. Tissues from the reduced lobes of each treatment animal were also stained with standard trichrome techniques. Lesions induced by the reduction sleeves in the involved lungs were graded for pleural fibrin deposition and superficial pleuritis, parenchymal compression and vascular compromise, partial infarction, or complete infarction of the lungs.

Statistical Analysis

Compliance data were analyzed using repeated-measures analysis of variance (ANOVA) model including one grouping factor (treatment group, experimental or control) and two within factors (weeks and volumes that pressure measurements were taken). Data for FRC and Dlco were analyzed using ANOVA with repeated measures. Data were analyzed using standard statistical software (Systat 8.0 and BMDP; SPSS; Chicago, IL).

Results

Development of Emphysema

As expected, animals generally tolerated emphysema induction reasonably well. Two of 22 rabbits died during emphysema induction (10%). On average, moderate degrees of emphysema developed histologically and by pulmonary function testing (see below).

Surgical Procedure

The surgical procedure was well tolerated by all animals. The LVR was quickly and easily applied. The device was readily reloaded for multiple lobe applications.

Complications and Air leak

There was no detectable air leak in any animal undergoing LVR with the volume reducer or sham surgical animals in this study. All animals recovered from LVR surgery, without operative or perioperative mortality.

FRC

At baseline, the average FRC for the control group was 33.75 mL (SEM, 0.88 mL) and 30.87 mL (SEM, 1.23 mL) for the experimental group. These values were not significantly different from each other at baseline (p = 0.07). At 6 weeks, when emphysema developed, the average FRCs for the control group and experimental groups increased to 34.86 mL (SEM, 2.44 mL; p = 0.71) and 33.63 mL (SEM, 1.27 mL; p = 0.06), respectively. Again, the experimental and control emphysema animal FRC values were not significantly different from each other (p = 0.66). At 7 weeks (1 week after surgery), the average FRC decreased significantly in the experimental group to 25.36 mL (SEM, 2.49 mL; p = 0.005) but showed no change in the control group following surgery (32.0 mL; SEM, 2.37 mL; p = 0.50). There was also a significant difference (p = 0.04) when comparing FRC of the experimental and control group at week 7. These findings are consistent with development of similar degrees of emphysema in both groups following elastase nebulization, with significant reduction in lung volume after surgery only in the LVR-treatment group.

Compliance

Compliance curves (pressure volume curves) adjusted for FRC were plotted for both of the groups (control and experimental) at each of the study times (baseline, emphysema week 6, and final study week 7; Fig 4). Analysis of the data using a repeated-measures ANOVA model showed no difference between groups at baseline (p = 0.27). With emphysema at week 6, the curves significantly shifted up to the left as the lungs became "more compliant" (less elastic) in both groups (p = 0.03). At the final study date (week 7), the curve in the experimental group significantly shifted down to the right after LVR compared to presurgery week 6 (p = 0.002), showing "decrease in compliance," while the curve in the control group remained unchanged (p = 0.30).

Dlco

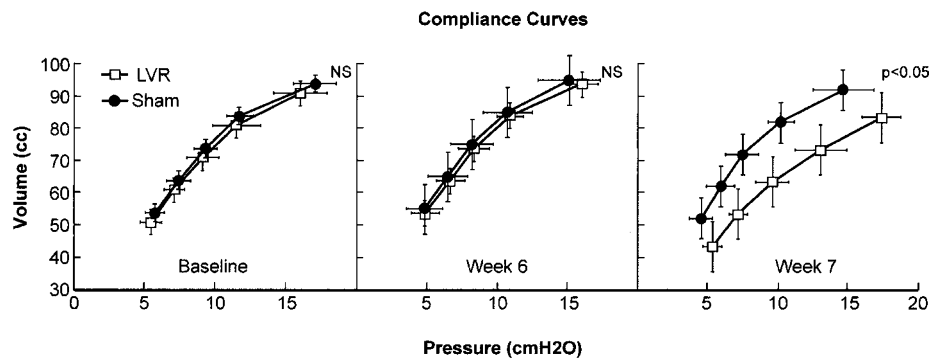Dlco changed in control-group animals from 0.66 mL/mm Hg/min (SEM, 0.04 mL/mm Hg/min) at

FIGURE 4. Static respiratory system compliance. Graph shows lung compliance at baseline before induction of emphysema, preoperatively (week 6) after induction of emphysema, and postoperatively (week 7) 1 week after surgery.

baseline (before emphysema), to 0.55 mL/mm Hg/min (SEM, 0.08 mL/mm Hg/min) after emphysema induction, and then to 0.6 mL/mm Hg/min (SEM, 0.05 mL/mm Hg/min) 1 week after sham surgery (week 7). In the experimental-treatment group, the DLCO values went from 0.66 mL/mm Hg/min (SEM, 0.11 mL/mm Hg/min) at baseline, to 0.54 mL/mm Hg/min (SEM, 0.05 mL/mm Hg/min) after emphysema induction, to 0.49 mL/mm Hg/min (SEM, 0.05 mL/mm Hg/min) 1 week after LVR surgery (week 7). None of these differences were statistically significant (Table 1).

Histology

Lungs from all rabbits had some degree of emphysema characterized by disruption of the alveolar walls with formation of extended open airspaces. The diffuse alveolar emphysema ranged from mild to moderate in all rabbits.

Thirty regions were reduced by LVR devices in 10 experimental animals. The lobes that were reduced showed pleural reaction, parenchymal compression, and vascular compromise that resulted in complete infarction of only the reduced lung tissue in the worst cases. The reduced middle lobe of the right lung had some degree of infarction in 5 of 10 LVR-treated animals, while the upper lobe of the right lung and upper lobe of the left lung each had infarction in 3 of 10 animals. There were no other obvious differences in other pleural or parenchymal reactions.

Changes in nonreduced lobes and in sham-operated control animals consisted of pleural tags and plaques, fibrinous and fibrous, and a predominantly mononuclear inflammatory infiltration. These changes, also being present in sham-operated animals, probably represent reaction to the trauma of open thoracic surgery. Histology samples are shown in Figure 5. In summary, the reduction of lung lobes caused pleuritis of variable degree, and vascular compromise with infarction.

DISCUSSION

Clinical investigations continue to refine LVRS for patients with advanced emphysema. LVRS produces improvements in pulmonary function test results and quality of life when performed in selected patients, with greatest improvement reported in patients with predominantly upper lobe, heterogeneous presentations.[31–38]

Emphysema leads to pulmonary and thoracic hyperexpansion resulting from loss of lung elastic recoil. Increased lung elastic recoil has been demonstrated following resection of severely diseased lung regions during LVRS and may be a major mechanism of improvement in lung function.[5,7,8,10,11] LVRS is generally performed with buttressed staple excision, but is still complicated by a substantial incidence of prolonged air leaks.[18,19,21–23] When minimal postoperative air leaks persist, patients may be discharged with Heimlich valves connected to chest tubes.[23,24] Improved methods for rapid, simple, and effective LVRS with reduced morbidity would enhance the potential applicability of LVRS for emphysema treatment. This study was designed to investigate an approach to LVRS using a vacuum-applied silicone elastomer LVR in an emphysema animal model. This approach does not require tissue resection, potentially reducing air-leak risks and facilitating the procedure.

Previous published studies[26–28] using this elastase rabbit emphysema model have demonstrated increased FRC and decreased elastic recoil (compliance) analogous to human disease, with improvements back toward baseline in subjects following LVRS. In this study, induction of emphysema produced the expected moderate increases in FRC and an upward shift of the compliance curves, interpreted as an increase of lung volume with concomitant decrease in lung elastic recoil. The animals treated with the LVR device had a decrease in FRC by reduction of lung volume resulting from compres-

FIGURE 5. Histology of elastase-induced emphysema. *Left, A*: Changes produced in the emphysematous lung tissue 1 week after LVR surgical implant. Lung tissue is compressed (reduced). *Right, B*: Changes produced by emphysema in a nonreduced area in the same animal (hematoxylin-eosin, original × 10 for both photomicrographs).
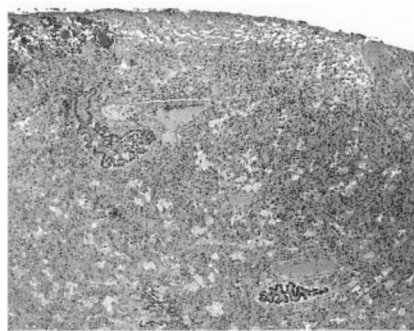
Reduced lung tissue
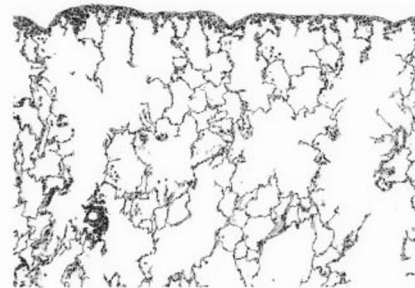
Non-reduced lung tissue

sion of the treated segments of emphysematous lung tissue. This was accompanied by a downward shift in the compliance curve that actually shifted even beyond the pre-emphysema values. Increased static respiratory system recoil pressures suggest increased recoil of the remaining lung following LVR treatment (as chest wall effects on respiratory system compliance are minimal in the rabbit).[39] As expected, no changes were observed after surgery in the sham control emphysema animal group. Since no lung tissue was resected in the experimental LVR-treated group, the observed reduction of the emphysema-induced elevation of FRC and improved elastance may be related to the compression and encapsulation of segments of the reduced diseased lung tissue, increasing tractional forces in thoracic space for the remaining nonreduced segments. There was minimal histologic effect on the adjacent lung.

Previous studies[25,26,29] in this animal model have shown a correlation between the quantity of excised lung mass with the magnitude of reduction in FRC and downward compliance curve shift. Following LVR treatment with the silicone elastomer in this study, compliance curves in the treated animals shifted downward beyond the baseline pre-emphysema values. Such dramatic effects may be may be indicative of more extensive effective lung reduction produced by these devices. The results obtained in this study of moderately emphysematous animals suggest that the implantable devices reduced an adequate amount of tissue to produce improvements in FRC and compliance curves without adversely affecting DLCO. The downward and rightward shift of the compliance curves after LVRS, beyond baseline levels, probably represents an "overshooting" due to excessive reduction from the mildly hyperinflated state. The magnitude of the downward shifts were generally larger than we have seen with maximum tolerable staple LVRS. We suspect this may be a demonstration of the effectiveness of the LVR capabilities. However, concerns arise regarding possible excessive restrictive physiology after LVRS with this device.

The clear, transparent devices and vacuum chamber allowed the surgeon to selectively capture and reduce emphysematous tissue. The ability to incrementally reversibly increase or decrease the amount of lung tissue reduced during surgery by implanting more devices or removing devices may be a potentially distinct advantage of this novel approach. Unlike current LVRS resection methodology, implanted silicone elastomer devices can be readily removed after initial implantation until their final fixation to the lung, if the implant is found to be malpositioned, or result in excessive lung tissue reduction.

The use of the implantable LVR in this animal model produced no perioperative or postoperative air leaks in the animals studied. The absence of air leaks and minimal bleeding may be associated with the compression of the tissue produced by the device deforming the airways and blood vessels and increasing resistance to flow of both blood and air. The rapid lung reduction using the vacuum-assisted device and absence of perioperative and postoperative air leaks reduced the operative time and facilitated postoperative recovery, as none of the animals required extended use of chest tubes. While the effects of the LVR in this study were compared to sham animals, not directly to staple methods, air leaks have been previously observed in this animal model of emphysema when LVRS was performed using staples.[25,26,28,29] In this animal emphysema model, the postoperative mortality of standard staple LVRS has been found to be approximately 20%, mostly related to air leak and pneumothorax. There were no operative or postoperative deaths in the 10 animals in the current study using the silicone LVRs.

Histologic findings of this model demonstrate moderate emphysema produced by the multiple nebulizations of elastase. In this study, similar findings were seen with some degree of alveolar destruction evident in all animals and observed in all regions of lung tissue, particularly in subpleural locations. The areas of lung reduced by the LVR device exhibited relatively mild pleural reaction, with extensive parenchymal and vascular compression that resulted in cellular infarction in the reduced lung tissue within the silicone implant. Changes in non-reduced lobes and in sham-operated control rabbits consisted of similar mild pleural inflammatory reaction, probably as a response to the surgical intervention. We observed the expected effects of the LVR device in compressing the tissue parenchyma, airways, and circulation, which produced an ischemic and inflammatory response on the tissue without compromise of the neighboring structures. In the short-term follow-up period of this study, no adverse effects of the compressed, necrotic lung tissue were observed. There was no evidence of localized or systemic infection, hemorrhage, or delayed pneumothorax that are of potential concern. We hypothesize that the reduced, ischemic tissue will fibrose over time, though long-term studies will be needed to confirm this speculation.

There are a number of limitations of the current study in this rabbit model. Despite the multiple nebulizations, the degree of emphysema is moderate, not nearly as severe as end-stage disease seen in humans. Only objective function is measured, subjective response cannot be assessed. The disease is acute, and some of the manifestations of long-

standing emphysema are not observed. The LVR devices were implanted for only 1 week, with evaluation of only short-term effects produced by the interventions. The animals do not have evidence of bronchitis, infection, or pulmonary vascular abnormalities that may increase operative risks and postoperative complications, particularly with a foreign body implant, long-term follow-up, and with retained "necrotic" lung tissue. The number of animals studied is relatively small, and complications occurring at relatively low incidence levels may not have been encountered. Additionally, the incidence of air leak with LVRS may be underestimated because of the relatively mild degree of parenchymal lung disease induced. Longer-term implants and larger animal studies will be needed to provide further information regarding the potential applicability, safety, and effectiveness of this technique. Nonetheless, despite these limitations, there are a number of analogous aspects of this LVR animal investigation that suggest potential for this novel concept of elastomer reducer methods for human emphysema treatment.

In conclusion, in this short-term study, we found that the implantable LVR device produced safe and effective lung volume reduction in this animal emphysema model. Beneficial changes in FCR and compliance were accomplished without tissue resection. The procedure was fast and subjectively simple, producing minimal morbidity, no mortality, and no observed air-leak complications in the treated animals in this model. Future research is required to assess long-term effects and complications, and to investigate the feasibility of this method for lung volume reduction.

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