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Journal

Journal of Surgical Research, 92(2)

ISSN

0022-4804

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Publication Date

2000-08-01

DOI

10.1006/jsre.2000.5846

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Pulmonary Vascular Pressures Increase after Lung Volume Reduction Surgery in Rabbits with More Severe Emphysema¹

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Submitted for publication June 1, 1999

Background. Emphysema is a chronic disease of the lungs with destruction of terminal alveoli and airway obstruction. Lung volume reduction surgery (LVRS) is being investigated for the treatment of emphysema. Increasing resection volumes with LVRS may lead to worsening of carbon monoxide diffusing capacity (DLCO) despite improvement in compliance and flow. We hypothesized that the pulmonary circulation-related parameters, pulmonary artery pressure (PAP) and diffusing capacity (DLCO), may be used as indicators of the maximally tolerated LVRS resection volume.

Methods. Emphysema was induced in 55 rabbits by endotracheal nebulization, with either single 15,000-unit (mild emphysema) or three 11,000-unit (moderate emphysema) doses of elastase. At Week 6, bilateral LVRS was performed via median sternotomy with an endoscopic stapler. Single-breath DLCO, static compliance, and PAP were measured prior to emphysema induction, preoperatively, and 1 week following LVRS. Animals were divided into the following groups: Group I (mild emphysema, <3 g resected), group II (mild emphysema, >3 g resected), group III (moderate emphysema, <3 g resected), group IV (moderate emphysema, >3 g resected).

Results. All animals having LVRS had immediate postoperative increase in pulmonary vascular resis-

tance (PVR) following lung resection. Mean PAP, however, remained elevated when measured 1 week after LVRS (sacrifice) in animals with moderate emphysema. This is in contrast to animals with mild emphysema, in which follow-up PAPs approached preoperative baseline.

Conclusion. These finding suggests that sustained increased PVR, denoted by elevated PAP, is more likely to occur after LVRS in animals with more severe emphysema and larger volume resection. The spirometric and compliance benefits of greater resection volumes have to be weighed against the compromise in pulmonary vasculature in the effort to determine the ideal resection volume for various degrees of emphysema. © 2000 Academic Press

Key Words: lung volume reduction surgery; pulmonary artery pressure; pulmonary hypertension.

INTRODUCTION

The benefits and limitations of lung volume reduction surgery in the treatment of emphysema are progressively being elucidated in laboratory and patient investigations. Extensive efforts are underway to determine methods for optimizing resection volumes for LVRS patients. Current LVRS procedures remove "approximately twenty to thirty percent" of the lung volume at the time of operation with variable responses to surgery. However, little information is available regarding how optimal resection volumes are achieved and whether the operation needs to be tailored to each patient according to more defined parameters. Physiologic variables that might limit resection may include pulmonary vasculature and diffusing capacity. Previous laboratory experience has correlated the degree of compromise in diffusing capacity after lung volume

Presented at the 23rd Annual Symposium of the Association of Veterans Administration Surgeons, St. Louis, Missouri, May 2-4, 1999

¹ Supported by DOE Grant DE-FG03-91ER61, ALA Grant CI-030-17, California Tobacco Related Disease Research Program (CTRDRP) 6RT0158, and American College of Surgeons Faculty Research Grant.

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reduction surgery with escalating volumes of lung resected [1, 2].

Diffusing capacity in severe emphysema is influenced by the available gas-exchanging alveolar surface area, ventilation-perfusion matching, and functional pulmonary capillary surface and volume. Decreased pulmonary capillary volume and chronic hypoxemia may be associated with varying degrees of pulmonary hypertension in patients with advanced emphysema. For these reasons, we hypothesized that (1) pulmonary artery pressures will rise with more extensive pulmonary resection, and (2) more severe emphysema may be associated with a greater rise in pulmonary artery pressure (PAP) and deterioration in diffusing capacity (DLCO) following LVRS. Such rises in PAP could potentially be used as guides to assess optimal lung resection volume.

In this study, we investigated the effects of large- and small-volume bilateral staple resection LVRS on intraoperatively measured PAPs and DLCO in rabbit models of mild and moderately severe emphysema. We analyzed changes in PAP, DLCO, and compliance in an attempt to identify potential intraoperative indicators for limits of resection in LVRS.

METHODS

This protocol was approved by the ALAC and the Institutional Animal Care and Use Committee at the University of California, Irvine. All rabbits were cared for in accordance with the NIH Guidelines for the Care and Use of the Laboratory Animal.

Animal Preparation

Fifty-five rabbits (3.0–4.5 kg) were anesthetized with a 2:1 mixture of ketamine-HCl (100 mg/ml):xylazine (20 mg/ml) at a dose of 0.75 ml/kg im. The rabbits were intubated with a 3-mm endotracheal tube and mechanically ventilated (Harvard Apparatus Dual Phase Control Respiratory Pump—Canine, Harvard Co., South Natic, MA) with tidal volume of 50 ml and frequency of 30–40/min. A 20-gauge intravenous catheter was placed in a marginal ear vein for intravenous access. Anesthesia was maintained with 0.3 ml of a 1:1 mixture of ketamine HCl (100 mg/ml):xylazine (20 mg/ml) given as an intravenous bolus as needed to maintain apnea throughout all procedures [1].

Induction of Emphysema

Emphysema was induced in 55 rabbits under general anesthesia by aerosolizing porcine elastase (Product E1250, Sigma Chemical Co., St Louis, MO) through the endotracheal tube over approximately 1 h. Mild emphysema was induced by a single nebulization dose of 15,000 units of elastase, while moderately severe emphysema was induced by three separate nebulizations of 11,000 units of elastase over a 4-week period. The nebulizer (Respigard, Marquest Medical Products, Inc., Englewood, CO) was placed in the inspiratory arm of the ventilator circuit with the tidal volume provided by the ventilator set at zero with the rate of 30 breaths/min. The O₂ flow through the nebulizer was adjusted to maintain the peak airway pressure at 20 cm H₂O, monitored by a pressure gauge placed at the side port of the endotracheal tube, which provided the tidal volume during induction [1].

Pulmonary Function Testing

Lung function measurements (lung volumes, expiratory flows, DLCO, compliance) were obtained at baseline prior to induction of emphysema, immediately before surgery at 4 weeks following induction of emphysema, and 1 week after surgery [1] as follows.

Gas dilution lung volumes. The inhalation gases consisted of 93% helium, 26% oxygen balanced with nitrogen, 0.87% C₂H₂, and 0.28% C₁₈O (Liquid Carbonics Corp., Los Angeles, CA). All gas concentrations were measured continuously by an on-line mass spectrometer (MGA 1100, Perkins–Elmer Corp., Pomona, CA). Analog data were converted to digital information by an AD converter (Keithley System 570, Cleveland, OH) sampling at 20 Hz and stored on an IBM Personal Computer.

The anesthetized and intubated rabbits were taken off the ventilator and placed in a left decubitus position. The sampling tube of the mass spectrometer was connected to the side port of the orotracheal tube through which the inspired and expired gas concentrations were continuously measured. A syringe was filled to 60 cc with inhalation gases and connected to the endotracheal tube. A multi-breath helium dilution maneuver was performed by manually insufflating and removing 50 cc tidal volume with the syringe for 10 breaths at an approximate rate of 20–30 breaths/min. The initial and final helium concentrations were used to calculate the functional residual capacity (FRC). Two measurements of FRC were obtained at each trial and averaged. The rabbits were returned to mechanical ventilation following each procedure [1].

Single-breath carbon monoxide diffusion capacity. Five-second breath-hold DLCO maneuvers were performed following the above FRC measurement on each rabbit. All gas concentrations were measured continuously through the mass spectrometer. Sixty cubic centimeters of the inhalation gas was insufflated into the lung through the endotracheal tube and held for 5 s. Thirty cubic centimeters of the inspired volume was then withdrawn and held to measure the gas concentrations at 33% expired volume. All data were sampled and digitized at 20 Hz.

For analysis, the breath-hold time was measured from 0.5 s from the start of inspiration to 30 cc of exhalation. The duration of inhalation was rapid and peak concentrations were achieved within 1 s. The initial helium and C¹⁸O concentrations were measured at their respective concentration plateaus following gas insufflation. The final gas concentrations were measured at 30 cc exhalation. DLCO was calculated from the standard formula and corrected to STPD. Adjustments were made for the rabbit body temperature and water vapor pressure [1].

Lung Volume Reduction Surgery

LVRS was performed 5 weeks following the first elastase induction of emphysema. The anesthetized and intubated rabbits were shaved and placed in a supine position. A total of 55 rabbits, induced with mild or moderate emphysema, underwent lung volume resection of between 2 and 6 g of lung tissue (0 g resected for controls).

Hypothermia was prevented with a surgical warming pad, and lactated Ringers solution was infused through an intravenous catheter in a marginal ear vein at 5–15 ml/h. The rabbits were mechanically ventilated. Oxygen saturation (Ohmeda Biox 3700 Pulse Oximeter, BOC Health Care), tidal CO₂ (Olimea 5200 CO₂ Monitor, BOC Health Care), and EKG (Hewlett Packard 78353B Continuous EKG Monitor, BioMedical Services) were monitored continuously.

The chest was shaved, prepped with Betadine, and draped sterilely. The thorax was entered through a median sternotomy. Bilateral upper and middle lobes were excised using a linear thoroscopic stapler Endopath ELC, Ethicon Endo-Surgery) with 3.5-mm staples. The target quantity of lung tissue removed was 2–6 g. The quantity of excised lung weight was carefully escalated. The excised lung tissues were weighed (wet weight, including attached staples) intraoperatively to assess adequate resection within the targeted

2–6 g range. In the sham operations, no lung tissue was excised. Hemostasis was obtained and a 12-French neonatal chest tube was placed under direct visualization into each pleural space. The two chest tubes were connected to 10 cm H₂O suction. The sternum was closed with O silk and the chest wound closed in layers with absorbable monofilament sutures. The rabbits were awakened from anesthesia and extubated. There was usually a small air leak in the chest tubes but all leaks sealed spontaneously within 1 h. All chest tubes were removed within 1 h [1].

Pulmonary Artery Pressure Measurement

Pulmonary artery pressures were measured in all 55 animals by using a cardiac monitor (Hewlett Packard 78353B Continuous EKG Monitor, BioMedical Services) connected to a transducer attached to a standard pressure saline bag. The saline bag pressure was raised to 200 mm Hg and then the transducer was zeroed at the level of the pulmonary artery and calibrated. After the median sternotomy was performed and the catheter zeroed, the measurement was taken by using a 24-gauge catheter. Pulmonary artery pressures were measured while the thorax was open. The catheter was inserted into the right ventricular outflow tract and advanced into the pulmonary artery. When the characteristic pulmonary artery waveform was visualized on the monitor the measurements were obtained. Pulmonary artery pressure measurements were performed before and after lung resection, intraoperatively, and at sacrifice 1 week later [1]. Measured pressure parameters included the systolic and diastolic PAP. The mean PAP was calculated using the standard formula

$$\text{MPAP} = (2\text{PAD} + \text{PAS})/3.$$

Histologic Preparation

The animals were sacrificed 1 week following LVRS. After sacrifice, the lungs were removed *en bloc* and inflated with formalin through the trachea at 20 cm H₂O pressure for 24 h for histologic preparation. The lung sections were prepared at 0.2- to 0.4-cm thickness and embedded in paraffin. Slides were stained with hematoxylin and eosin and studied by light microscopy.

Animal Analysis Groups

Animals were separated into four groups for analysis. Group I consisted of animals that had a single nebulization of elastase (mild emphysema) receiving small lung resection volumes of less than 3 g of tissue.

Group II consisted of animals with a single nebulization of elastase (mild emphysema) receiving large lung resection volume of greater than 3 g.

Group III comprised animals with multiple nebulizations of elastase (moderate emphysema) receiving small resection volumes of less than 3 g.

Group IV consisted of animals with multiple nebulizations of elastase (moderate emphysema) with large lung volume resections of greater than 3 g.

Statistical Analysis

All helium-dilution-lung-volume, compliance, flow and DLCO data for each rabbit were tabulated corresponding to baseline, preoperative, and postoperative measurements. Comparisons of baseline to preoperative values and preoperative to postoperative values were made using paired two-sample ANOVAs. Comparison of response to surgery, based on treatment groups, was made using unpaired two-sample ANOVA. A standard statistical software program was used for all statistical analysis (Systat 7.0, SPSS Inc.). The changes in DLCO from preoperative to postoperative data were analyzed and graphed in relation to the excised lung weights.

RESULTS

All deaths occurred from large resections of greater than 3 g of lung tissue, in both the single- and multiple-induction animals (Groups II and IV). No postoperative deaths occurred in either of the small resection groups (Groups I and III). The postoperative mortality within the single-induction, large-resection group (Group II) alone was 24% compared with 28% for the multiple-induction large-resection group (Group IV). In general, resected lung volumes of all 55 animals ranged from 1.9 to 6.39 g. Animals of Group I, single nebulization and small volume resection, had a mean resection volume of 2.31 g (± 0.30 g). Single-nebulization animals that survived large resections (Group II) had a mean resection volume of 4.34 g (± 0.63 g). In the multiple-nebulization groups, the small volume resections (Group III) averaged 2.29 g (± 0.39 g), while the large-volume resections (Group IV) averaged 3.77 g (± 0.73 g). Postoperative deaths tended to occur within 3 days of surgery. All mean values are reported with the SEM. In all cases, autopsies revealed pneumothorax as the cause of postoperative death.

Pulmonary Artery Pressure

Systolic PAP. Systolic PAP were measured in all rabbits intraoperatively before and after lung resection and at sacrifice. The values are reported as means with SEM. As a result of lung resection, Group I showed a trend of immediate increase in average systolic PAP by 5.00 mm Hg (± 1.7 mm Hg), followed by a decline in average pressures at sacrifice by 8.00 mm Hg (± 2.11 mm Hg). In contrast, Group II showed a trend of greater immediate increase in average systolic PA pressure by 7.40 mm Hg (± 1.68 mm Hg). One week following surgery, the average systolic PAP decreased by 5.22 mm Hg (± 2.45 mm Hg). In a comparison of moderately severe emphysema groups, Group III exhibited an increase in mean systolic PAP of 3.78 mm Hg (± 0.84 mm Hg) versus the 3.52 mm Hg (± 0.80 mm Hg) increase in Group IV. During the postoperative recovery period, Group III showed a trend of greater decrease in average systolic PAP back toward preoperative values (2.89 ± 0.98 mm Hg) in comparison to Group IV (0.78 ± 1.62 mm Hg) (see Table 1).

Mean PAP. The mean PAP in all groups increased immediately after LVRS and then decreased from LVRS to surgery (see Fig. 1). The average increase in mean PAP, from pre-LVRS to post-LVRS, in Group I was 3.12 mm Hg (± 1.70 mm Hg), while in Group II the average increase was 5.2 mm Hg (± 1.55 mm Hg). The average decline in mean PAP, from post-LVRS to sacrifice, in Group I was 7.13 mm Hg (± 1.65 mm Hg), while that of Group II was 2.85 mm Hg (± 1.90 mm Hg) (see Table 1). The change in mean PAP from pre-LVRS to post-LVRS tended to be greater in Group II than in

TABLE 1
Pulmonary Artery Pressures in Large- and Small-Volume LVRS

	Group I			Group II				
	Pre-LVRS (n = 10)	Post-LVRS (n = 9)	Sacrifice (n = 9)	Pre-LVRS (n = 11)	Post-LVRS (n = 10)	Sacrifice (n = 10)		
Systolic pressure (mm Hg)	16.40 ± 1.14	22.50 ± 1.50	13.25 ± 1.18	17.70 ± 1.66	25.50 ± 2.20	19.00 ± 0.76		
Diastolic pressure (mm Hg)	8.00 ± 1.05	10.25 ± 0.99	5.75 ± 0.86	8.60 ± 1.19	12.60 ± 1.70	9.90 ± 0.50		
Mean pressure (mm Hg)	10.82 ± 1.02	14.33 ± 1.11	8.25 ± 2.32	11.67 ± 1.29	16.90 ± 1.82	12.93 ± 0.41		
Statistical significance	Between pre- and postoperative $P > 0.05$		Between postoperative and sacrifice $P > 0.05$		Between pre- and postoperative $P = 0.005$		Between postoperative and sacrifice $P > 0.05$	
	Group III			Group IV				
	Pre-LVRS (n = 20)	Post-LVRS (n = 20)	Sacrifice (n = 17)	Pre-LVRS (n = 19)	Post-LVRS (n = 19)	Sacrifice (n = 17)		
Systolic pressure (mm Hg)	14.87 ± 0.61	18.33 ± 0.77	15.41 ± 1.06	15.20 ± 1.00	18.72 ± 1.01	17.68 ± 1.63		
Diastolic pressure (mm Hg)	7.50 ± 0.61	7.64 ± 0.74	7.41 ± 0.73	8.00 ± 0.99	8.86 ± 0.79	9.18 ± 0.83		
Mean pressure (mm Hg)	9.96 ± 0.59	10.90 ± 0.54	10.07 ± 0.79	10.40 ± 0.95	12.15 ± 0.80	12.01 ± 0.82		
Statistical significance	Between pre- and postoperative $P > 0.05$		Between postoperative and sacrifice $P > 0.05$		Between pre- and postoperative $P = 0.012$		Between postoperative and sacrifice $P > 0.05$	

Group I (ANOVA, $P = 0.23$) (see Fig. 1). Average increase in mean PAP, from pre-LVRS to post-LVRS, in Group III was 0.94 mm Hg (± 0.71), while that for Group IV was 1.75 mm Hg (± 0.63). The slight decline in mean PAP, from post-LVRS to sacrifice, was greater

in Group III than in Group IV. Group III trended downward by 0.77 mm Hg (± 0.59 mm Hg) while Group IV was by 0.24 mm Hg (± 0.98 mm Hg). Resultant mean values are reported with their SEM (see Table 1). In the emphysematous animals undergoing small-

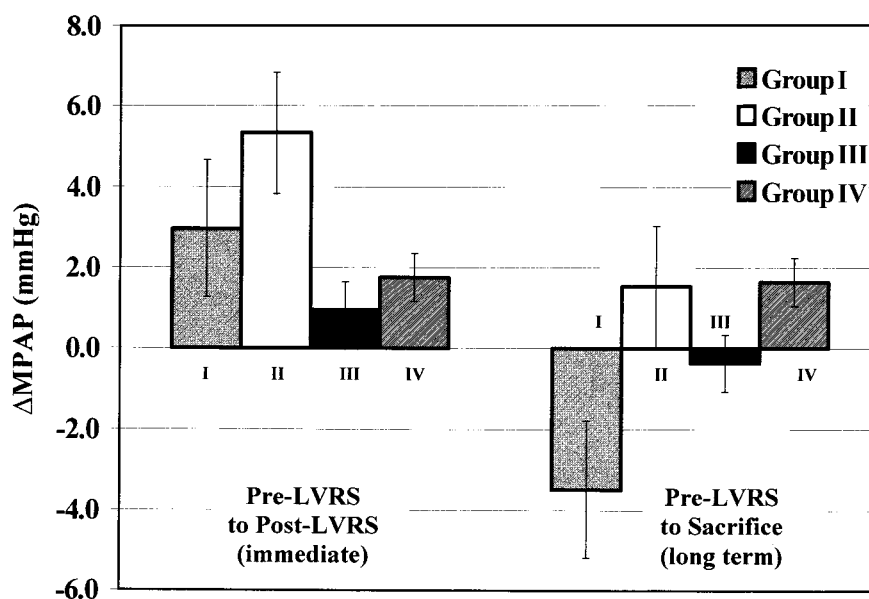


FIG. 1. Change in mean PAPs after surgery in all groups. The first data demonstrate the change in mean PAP (MPAP) from pre-LVRS to immediately after LVRS (GI $P = 0.125$, GII $P = 0.005$, GIII $P = 0.201$, GIV $P = 0.012$). The second data demonstrate the long-term change in MPAP from pre-LVRS MPAP to the sacrifice MPAP, 1 week later (GI $P = 0.116$, GII $P = 0.347$, GIII $P = 0.696$, GIV $P = 0.214$).

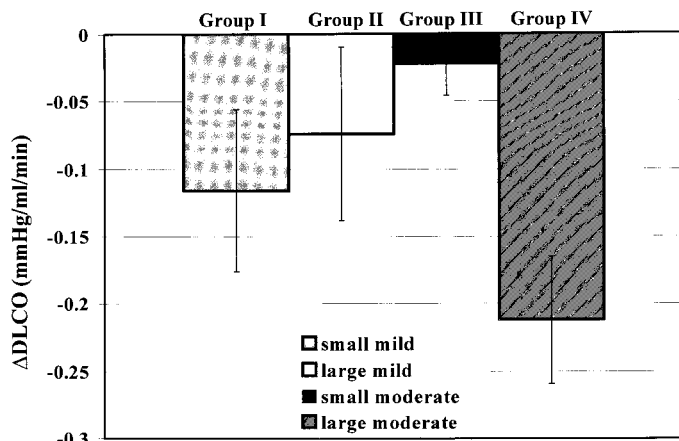


FIG. 2. Compromise in diffusing capacity (DLCO) after LVRS in all groups. Significant decrease in DLCO is seen in Group IV, animals with moderate emphysema receiving large resection of >3 g of lung tissue (GI $P = 0.09$, GII $P = 0.278$, GIII $P = 0.684$, GIV $P = 0.001$).

volume (<3 g) LVRS (Groups I and III), the intraoperative change in mean PAP immediately after LVRS was not significant in either the mild or moderate emphysema animals. However, the rise in intraoperative mean PAP after large-volume (>3 g) LVRS was statistically significant in both the mild and moderate emphysema groups, Groups II (ANOVA, $P = 0.005$) and IV (ANOVA, $P = 0.012$) (see Table 1).

Carbon Monoxide Diffusion Capacity

The single-breath DLCO decreased in all four groups after LVRS but the change reached statistical significance only in Group IV (moderate emphysema with large resection) (ANOVA, $P = 0.001$) (see Fig. 2). All mean values are reported with the SEM (see Table 2).

Compliance

Static respiratory system compliance at 60 cc above FRC was noted to increase with induction of emphysema and then decrease with LVRS in all groups. A greater increase was seen in the large-resection groups than in the small-resection groups after LVRS for both the mild emphysema animals (Fig. 3) and the moderate emphysema animals (Fig. 4). The changes were statistically significant in all groups at time of sacrifice [ANOVA: (Group I) $P = 0.011$, (Group II) $P = 0.001$, (Group III) $P = 0.001$, (Group IV) $P = 0.027$]. All mean values are reported with the SEM (see Table 2).

DISCUSSION

Lung volume reduction surgery is performed for palliation of severe emphysema with little objective information to guide the optimal volume of lung to be resected. Efforts have been made to target particular

areas of more advanced disease with preoperative imaging studies in heterogeneously distributed emphysema presentations. The major goal of this research study is to attempt to begin developing methods for determining optimal LVRS resection volumes for various severities of emphysema. Therefore, sham groups were included in this study since previous research from our laboratory has already established the significance of LVRS on mild and moderately severe emphysema animals [1, 2].

LVRS procedures are generally performed in high-risk patients, with acute mortality rates of 3–5% in most reports and morbidity approaching 10–20% in several studies [3–5]. Objective indicators for limits of resection are needed to optimize outcomes following LVRS. Previous animal studies have demonstrated that diffusing capacity tends to worsen with larger resection volumes and could potentially help guide volume limits of resection. However, DLCO is difficult to measure accurately intraoperatively for technical reasons (high inspired F_{IO_2} , mechanical ventilation) as well as operative conditions that may acutely decrease DLCO (atelectasis, bronchospasm, secretions, and positive-pressure ventilation). Therefore, we chose to investigate other potential intraoperative physiologic measures that may eventually be more applicable to LVRS outcome optimization.

Pulmonary capillary circulation, alveolar surface area and thickness, and ventilation–perfusion relationships determine DLCO. Since DLCO appears to be sensitive to LVRS volumes, we hypothesized that removal of excessive lung tissue would also result in impaired pulmonary circulation, manifested by increased pulmonary artery resistance and pressures. Pulmonary artery pressures can be measured intraoperatively and can be followed throughout the operative procedure.

Previous research in animals with mild emphysema has revealed an immediate acute rise in PAPs after LVRS, followed by a subsequent PAP return toward baseline levels 1 week after surgery. Thus, there appears to be little long-term effect on PAP in animals with mild emphysema. Experience with a more severe form of emphysema has yet to be tested in an animal model. Intuitively, we predict that more severe emphysema may require relatively greater resection volumes to demonstrate the benefits of the operation; however, greater resection volumes may be associated with decreased pulmonary vascular reserve. The purpose of this study was to determine whether the physiologic variables governing optimal resection volume for more severe emphysema were different from those in mild emphysema, and to assess the potential differences in effects of LVRS on DLCO in animals with more severe emphysema.

Our results show that there were no statistically

TABLE 2
Pulmonary Function Tests in Large- and Small-Volume LVRS

	Group I			Group II		
	Baseline	Preoperative	Postoperative	Baseline	Preoperative	Postoperative
DLCO	0.712 ± 0.21 (n = 9)	0.701 ± 0.17 (n = 9)	0.608 ± 0.13 (n = 8)	0.687 ± 0.19 (n = 11)	0.712 ± 0.18 (n = 11)	0.639 ± 0.13 (n = 9)
Statistical significance (DLCO)		Between pre- and postoperative <i>P</i> > 0.05			Between pre- and postoperative <i>P</i> > 0.05	
Static respiratory compliance	5.310 ± 1.207 (n = 9)	5.630 ± 0.708 (n = 9)	5.079 ± 0.787 (n = 9)	4.831 ± 0.442 (n = 11)	5.370 ± 0.696 (n = 11)	3.912 ± 0.461 (n = 8)
Statistical significance (compliance)		Between pre- and postoperative <i>P</i> = 0.011			Between pre- and postoperative <i>P</i> = 0.001	
	Group III			Group IV		
	Baseline	Preoperative	Postoperative	Baseline	Preoperative	Postoperative
DLCO	0.691 ± 0.189 (n = 14)	0.676 ± 0.116 (n = 14)	0.653 ± 0.199 (n = 14)	0.651 ± 0.144 (n = 13)	0.698 ± 0.143 (n = 13)	0.486 ± 0.116 (n = 13)
Statistical significance (DLCO)		Between pre- and postoperative <i>P</i> > 0.05			Between pre- and postoperative <i>P</i> = 0.001	
Static respiratory compliance	4.661 ± 0.440 (n = 10)	5.650 ± 0.549 (n = 10)	4.499 ± 0.673 (n = 10)	4.812 ± 0.401 (n = 6)	6.014 ± 1.193 (n = 6)	4.975 ± 0.881 (n = 6)
Statistical significance (compliance)		Between pre- and postoperative <i>P</i> = 0.001			Between pre- and postoperative <i>P</i> = 0.027	

significant changes in mean PAP immediately after LVRS with small resection volumes less than 3 g of lung tissue, in either mild or moderate emphysema. Only large lung tissue resections, greater than 3 g, resulted in significant elevation of mean PAP in both

mild and moderately severe emphysema. One week after LVRS, at the time of sacrifice, the mean PAP in the small-resection, mild emphysema animals (Group I) declined to values below the baseline pre-LVRS measurement. The large-resection, mild emphysema ani-

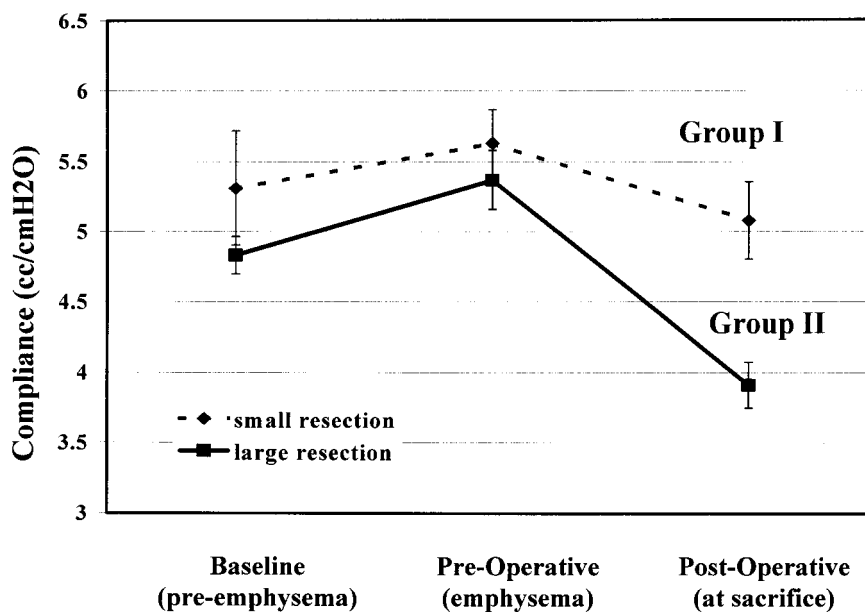


FIG. 3. Compliance after LVRS in animals with mild emphysema, in Groups I and II. The graph shows the compliance at baseline (before induction of emphysema), preoperative (after induction of emphysema), and postoperative (at sacrifice 1 week after surgery). Change in compliance between preoperative and sacrifice is statistically significant in both groups (GI *P* = 0.011, GII *P* = 0.001).

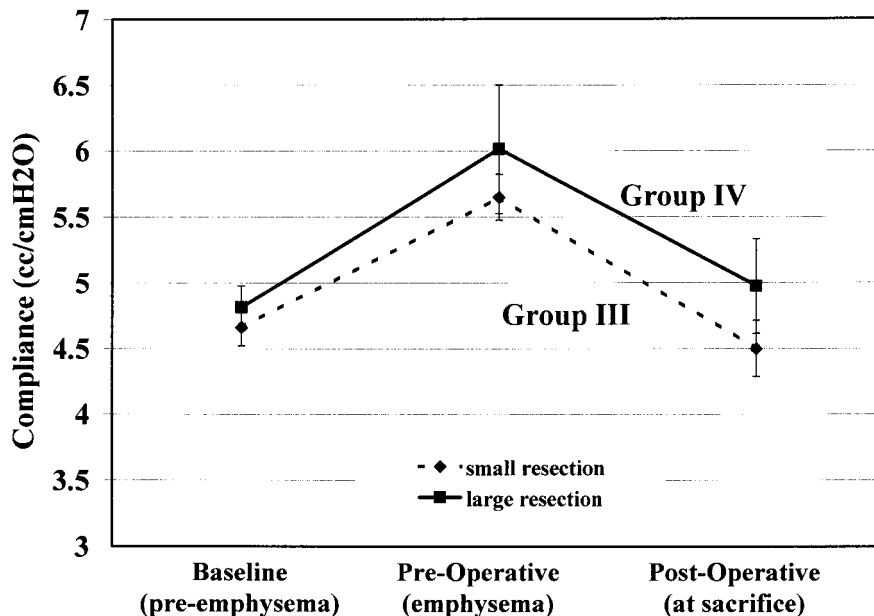


FIG. 4. Compliance after LVRS in animals with moderate emphysema, in Groups III and IV. The graph shows the compliance at baseline (before induction of emphysema), preoperative (after induction of emphysema), and postoperative (at sacrifice 1 week after surgery). Change in compliance between preoperative and sacrifice is statistically significant in both groups (GIII $P = 0.001$, GIV $P = 0.027$).

mals (Group II) approached baseline, but never quite reached pre-LVRS measurement.

The moderate emphysema animals, however, responded somewhat differently. Pulmonary artery pressures did not return to baseline following large- or small-volume resection (Group III and Group IV). Instead, mean PAPs of moderate emphysema animals remained relatively elevated. This suggests that animals with more advanced emphysema may be at risk for a greater incidence of sustained pulmonary hypertension after LVRS. The responses to large-volume resections in these more diseased animals also suggest that severity of pulmonary hypertension may correlate with resection volume.

West *et al.* [6] described alveolar crowding and collapse of pulmonary capillary beds with increased resistance to flow within the capillary vessels during positive-pressure exhalation. As the lungs expand during negative-pressure inspiration, the capillary walls have increased tractional support and pulmonary vascular resistance decreases. With LVRS, the removal of lung tissue functionally increases lung elastic recoil pressure, therefore decreasing intrathoracic pressure at equivalent lung volumes. This could account for some of the decrease seen in the PAP after the recovery period from LVRS following small-volume resections. However, with larger-volume resections, the lungs may no longer be able to compensate for the loss of capillaries by further increasing the capacitance of the remaining vessels. This could account for the rise in PAPs after recovery following the larger-volume resections. Therefore, if baseline emphysema is severe, we could

expect a greater compromise in DLCO after LVRS and might expect a higher incidence of pulmonary hypertension. This raises concerns about risks of potential sustained pulmonary hypertension and right-sided heart failure following excessive lung tissue removal, particularly in patients with very severe emphysema or preoperative pulmonary hypertension.

In this model, PAP elevations and decreases in DLCO that are seen following large-volume resections suggest that PAPs could indicate that maximal limits of larger-volume resection are being approached. However, there is a contrast between using PAP and DLCO as physiologic markers of the limits of LVRS. While PAPs rise with large-volume resections in both mild and moderate disease, DLCO decreases are seen only with large-volume resections in more severely emphysematous animals. The animals with mild emphysema tended to normalize their PAPs after a 1-week recovery period, which was less evident in animals with more severe emphysema, which tended to remain elevated above baseline pre-LVRS PAPs. Thus, PAPs may be a more sensitive indicator of resection volumes.

These findings contrast with concurrent compliance measurements, where larger-volume resections are associated with normalization of compliance curves. Thus, as we increase resection volumes in LVRS, the improvements in some physiologic parameters, such as compliance, must be weighed against deterioration in other parameters, such as DLCO and mean PAP.

Interestingly, in both mild and moderate emphysema, there is a trend, though not statistically significant, toward increased intraoperative mean PAPs im-

mediately following LVRS. If PAPs are to be a useful as intraoperative indicators of optimal extent of resection, methods must be developed for differentiating the extent of irreversible PAP rise from reversible intraoperative pressure rise. Standardizing inhalation to equivalent pressures (not volume) during PAP measurements, controlling for cardiac output and left ventricular filling pressures, or using bronchodilators or inhaled NO during PAP evaluations might require investigation as potential methods to help distinguish reversible from irreversible intraoperative PAP components.

While PAP may eventually be an intraoperative tool to help determine how much tissue to remove, there are a number of other serious limitations to this approach that can be seen from this study. First, all PAP measurements were made in anesthetized rabbits with open chests under positive-pressure ventilation. Such measurements may not accurately reflect the normal physiologic properties of the animals when the thorax is closed under negative-pressure inspiratory conditions. Second, the animals that received a single nebulization had normal PAPs before surgery despite emphysema. This may be due to the acute nature of the disease process since pulmonary hypertension may take considerable time to develop or may be indicative of a lower severity of emphysema seen in many operative patients. Third, all physiologic measurements were made at rest. Since PAPs are extremely dependent on cardiac output when capacitance reserve is exhausted, exercise PAPs may be much more critical determinants of resection volume limits than resting measurements. Finally, the animal model of emphysema that we developed is relatively diffuse and somewhat homogenous. Therefore, efforts in targeting specific areas of emphysema during resection are not addressed in this study. Clinically, nonuniform heterogeneous emphysema allows more targeted resection techniques. The effects of targeted resection of emphysematous lung tissues on PAPs and DLCO may or may not coincide with results found from our animal emphysema model. Future work is clearly needed to address these important issues.

Overall, this study has shown that pulmonary pressures rise and DLCO decreases following LVRS in an animal model. This is evident from the similar sustained elevations of mean PAPs at the time of sacrifice of mild and moderately severe emphysema animals,

although moderately severe emphysema animals experienced a lower immediate rise in mean PAPs following LVRS. The greater immediate rise in PAPs does not necessarily predict the longer-term effects of LVRS on PAPs. Therefore, further investigation on the usage of PAPs as an intraoperative indicator of the limits of LVRS on pulmonary functions and circulation is needed. Furthermore, this suggests that although a greater resection volume may be needed in animals with more severe emphysema to see a significant improvement in compliance, these animals may not be able to tolerate extensive resection because of the changes in diffusing capacity and pulmonary vasculature. This study also shows that the mortality rate associated with larger-volume LVRS is appreciably larger than that of small-volume resection: 24% (large resection) versus 0% (small resection) within the mild emphysema groups and 28% (large resection) versus 0% (small resections) within the moderate emphysema groups. This further supports the idea that there are limits to lung resection volume. However, a number of issues must be resolved in future investigations before the role of PAPs or other objective physiologic variables can be used clinically to guide resection extent in patients undergoing LVRS for palliation of severe emphysema.

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