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Respiratory Impedance following Bronchoscopic or Surgical Lung Volume Reduction for Emphysema

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Key Words
Respiratory system input impedance · Lung volume reduction surgery · Bronchoscopic lung volume reduction · Chest wall mechanics

Abstract
Background: Bronchoscopic methods for achieving lung volume reduction (BLVR) are presently undergoing clinical trials, and will soon be clinically available. Understanding the differential effects of surgical volume reduction therapy (LVRS) and BLVR on lung and chest wall physiology will assist physicians in selecting an optimal approach for patients. ***Objectives:*** Determine whether LVRS adversely affects lung or chest wall physiology at 3-month follow-up relative to BLVR in an experimental model of sheep emphysema. ***Methods:*** Twelve mixed-breed sheep were treated with papain to produce experimental emphysema, and were divided into control, LVRS, and BLVR treatment groups. Lung and chest wall impedance was measured at 0, 5, and 10 cm H_2O positive end-expiratory pressure at baseline and 3-month follow-up. ***Results:*** Emphysema was associated with increased airway resistance, decreased lung tissue resistance and elastance, and increased chest wall tissue resistance. Following treatment, equivalent increases in lung elastance occurred in the LVRS and BLVR groups compared to controls. LVRS did not adversely affect chest wall impedance despite causing extensive pleural scarring. ***Conclusions:*** (1) Experimental emphysema following prolonged papain exposure progresses after cessation of treatment. (2) BLVR and LVRS produced equivalent lung and chest wall impedance responses at 3-month follow-up. (3) LVRS did not adversely affect chest wall impedance despite being associated with extensive pleural scarring.

Introduction

Respiratory system impedance recorded in anesthetized paralyzed patients immediately before, and shortly after completion of lung volume reduction surgery (LVRS) indicates that the procedure causes a consistent, acute, and substantial increase in both lung and respiratory system impedance [1, 2]. While forced expiratory flow rates improve in a majority of LVRS patients by 3 months, the

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long-term effects of surgery on respiratory system impedance are unknown. Persistent adverse effects of surgery on lung impedance could blunt potential improvement from LVRS treatment, and shorten the duration of symptomatic benefit. A better understanding of the extent and persistence of initial adverse effects of LVRS on respiratory system mechanics would broaden our current understanding of the physiological mechanisms that determine a favorable response to this procedure. This is of particular relevance since new approaches have been developed that permit volume reduction to be accomplished nonsurgically [3–5]. In addition to being less morbid and less costly than LVRS, nonsurgical approaches to lung volume reduction might have physiological advantages over surgical treatment, if in fact they can successfully produce lung reduction without adversely affecting respiratory system impedance.

The present study compares lung and chest wall input impedance measurements at 3 months following LVRS and bronchoscopic lung volume reduction (BLVR) in sheep with moderate, anatomically homogeneous, experimental emphysema. Results indicate that despite extensive pleural scarring following LVRS, chest wall impedance in LVRS, BLVR, and sham-treated control animals is similar, indicating that LVRS does not cause any sustained adverse effects on respiratory system impedance.

Methods

Experimental Protocol

Twelve healthy mixed-breed nonpregnant ewes (weight 57.5 ± 4.3 kg) were studied in accordance with an animal study protocol approved by the Tufts University School of Veterinary Medicine Institutional Animal Care and Use Committee. All animals were acclimated to the testing facility and screened for zoonoses prior to study. Baseline measurements were recorded in endotracheally intubated, anesthetized animals to confirm normal respiratory mechanics prior to generation of experimental emphysema. Experimental disease was generated via administration of nebulized papain [4, 6, 7]. Baseline studies included measurements of:

(1) total lung capacity (TLC) and residual volume (RV) determined by whole body plethysmography in the prone position;

(2) single breath diffusing capacity (D_{Lco}) and alveolar volume (V_A);

(3) spiral CT images of the thorax from the thoracic inlet to the diaphragm performed at 25 cm H_2O positive end-expiratory pressure (PEEP);

(4) lung and respiratory system input impedance measured between 0.156 and 8.05 Hz using the optimal ventilator waveform (OVW) method of Lutchen et al. [8]. Chest wall impedance was calculated as the difference between respiratory system and lung impedance at each forcing frequency.

Sheep received 900 IU/kg of nebulized papain delivered during mechanical ventilation once per week for 10 consecutive weeks. Treatments involved delivery of nebulized papain over 30 min using a dual nebulizer system connected in-line with the mechanical ventilator [9]. Each animal received 5 puffs of albuterol sulfate prior to papain treatment to minimize bronchospasm.

After 4 weeks, animals were restudied in identical fashion, and randomized to one of three treatments (n = 4 in each): sham-bronchoscopy (control); BLVR, or LVRS. Treatments were performed within 2 weeks of randomization.

Control animals underwent bronchoscopy following administration of anesthesia and placement of an endotracheal tube, but received no BLVR treatments. BLVR animals received BLVR treatment, performed as previously described [4], at 10 subsegmental sites throughout the lungs. Since a subsegment communicates with approximately 1.5–2.0% of total lung volume, BLVR treatments were intended to produce a 15–20% lung volume reduction in each animal. LVRS was performed by a board-certified thoracic surgeon (either S.J.M. or M.T.J.) through a transverse sternal thoracotomy. General anesthesia, mechanical ventilator support, and continuous cardiopulmonary monitoring were maintained throughout the procedure [7]. Staple plication was performed at between 5 and 8 sites in the cranial and upper regions of the caudal lung lobes using a US Surgical T55 Endostapler to remove up to 80 g of lung tissue in amounts sufficient to produce a 15–20% reduction in overall lung volume. Bilateral 24 F chest tubes were placed following the procedure, and attached to Heimlich valves. Sterile occlusive dressings were applied to the sternal wound to prevent infection. Animals received analgesics (Buprenorphine 0.01 mg/kg i.v. every 8 h and Banamine 2 mg/kg i.v. every 12 h), and prophylactic antibiotics (Ceftiofur 6 mg/kg i.m.) for the first week following treatment. Chest tubes were removed on postoperative day 3.

Three months following treatment, each group was restudied as previously described. Following completion of physiological measurements and CT imaging, animals were euthanized with intravenous pentobarbital (100 mg/kg i.v.) and autopsied. Notable findings were documented photographically at the time of autopsy. A schematic of the protocol is shown in table 1.

Static Lung Physiology and CT Scan Densitometry Assessment

The severity and distribution of experimental emphysema in test animals were assessed following the development of experimental emphysema (EMPH time point) by comparing TLC, RV, D_{Lco}, D_L/V_A, and CT densitometry measurements to baseline values.

TLC was defined as the lung volume at 30 cm H_2O transpulmonary distending pressure calculated by fitting deflation quasi-static pressure-volume curves to the exponential expression of Salazar and Knowles [10]. Functional residual capacity (FRC) was assessed by whole body plethysmography during spontaneous breathing. The pressure at FRC, which was used to fix the end-expiratory pressure point for these measurements, was assessed from esophageal balloon recordings at passive exhalation with animals prone and lightly anesthetized. RV was defined as the volume of gas remaining in the lung when airway opening pressure was measured as equal to –25 cm H_2O during slow withdrawal of gas from the lung using a 3-liter syringe starting from FRC. D_{Lco} was measured by the single breath carbon monoxide absorbance test, and V_A by the single breath helium dilution test.

Table 1. Protocol summary

12 healthy female sheep enrolled	Baseline recordings[1] TLC, RV, D_{Lco}, CT imaging, Z_L, Z_{CW}	10 weeks of nebulized papain + 4 weeks of recovery	Experimental emphysema[1] TLC, RV, D_{Lco}, CT imaging, Z_L, Z_{CW}	*Control treatment* *BLVR treatment*[1] *LVRS treatment*[1]	Post-treatment[1] TLC, RV, D_{Lco}, CT imaging, Z_L, Z_{CW} followed by autopsy
2 week acclimation period	6–7 months		4 weeks		3 months
BAS			EMPH		TX

TLC = Total lung capacity; RV = residual volume; D_{Lco} = diffusing capacity; Z_L = lung impedance; Z_{CW} = chest wall impedance; BAS = baseline time point; EMPH = emphysema time point; TX = post-treatment.

[1] Time points at which experimental data were collected.

as previously described [4]. Each individual data point represents the average of two sequential measures.

CT densitometry was performed by digital analysis of thoracic images recorded using a spiral imaging technique with the lung inflated to +20 cm H_2O transrespiratory pressure. A computerized algorithm was used to define the border between lung and chest wall, with lung defined as any tissue with an HU of ≤150 U. Calculations were performed for sections at 1-cm intervals. Data for each animal are summarized as a single whole-lung average for all thirty image cuts, and results are summarized as mean value ± the standard deviation.

Input impedance Measurements

Measurements of input impedance of the lung and respiratory system were performed in anesthetized sheep receiving sufficient anesthesia to achieve apnea for >2 min. Animals were not paralyzed, however. Impedance determinations were made by recording airway flow and volume delivered through an endotracheal tube with the tip positioned 6–8 cm above the carina, airway pressure sampled through a catheter positioned 2 cm beyond the distal end of the endotracheal tube, and esophageal pressure sampled using a balloon catheter positioned beyond the thoracic inlet. Recordings were made with animals positioned prone in a specially designed cart with a central opening and cushioned-support that minimizes impingement of abdominal contents on the diaphragm. Heart rate and arterial saturations were monitored throughout testing.

Flow and volume were delivered according to a user-specified profile by a computer-controlled pneumatic ventilator with sufficient power to deliver physiologically relevant tidal volumes over a broad frequency range (10 ml/kg). Airway and esophageal pressure recordings were made using calibrated variable inductor pressure transducers (Celesco ± 25 cm H_2O transducers) with a common mode rejection ratio of <1%. Flow was measured with a Hans-Rudolf screen pneumotachometer linear over the flow ranges studied, and a calibrated linear pressure transducer (Celesco ± 2 cm H_2O transducer).

Input forcing was performed according to the optimal ventilator waveform method [8]. This method uses an input waveform composed of eight superimposed sine waves, in which peak flow rates are maintained below the turbulent range, and the frequencies of the different waves are selected to provide impedance estimates over a broad range (0.156–8.05 Hz) while simultaneously minimizing the potential for harmonic distortion.

Impedance results for both the respiratory system and lung were interpreted by fitting the frequency domain data to a single-port two-compartment model of the general form:

$$P(j\omega)/V(j\omega) = R + [G - Hj]/\omega^n + I\omega j$$

where P is pressure, V is flow, R is Newtonian resistance, G is the coefficient of tissue dissipation (proportional to tissue resistance), H is the coefficient of tissue elastance (proportional to dynamic elastance), I is inertance, ω is angular frequency = to $2\pi f$, and j is the unit imaginary number equal to $\sqrt{-1}$ [11]. Parameter estimates were obtained by fitting the real and imaginary parts of the measured impedance obtained from Fourier analysis to the model using an iterative scheme to minimize the root mean squared error between measured and estimated impedance values, expressed in terms of model parameters R, G, I, and H. Chest wall fits were performed omitting the inertance term, since chest wall inertance has been consistently shown to be negligible [12, 13]. Only values for which the coherence of model fits with the measured data was better than 0.95 were included in the results.

Tissue Stereology

Animals were euthanized with pentobarbital, exsanguinated, and the heart and lungs were removed en bloc. The right lung of each animal was cannulated, and the lungs were inflated to 25 cm distending pressure with 10% buffered formalin. After 30 min, the right mainstem bronchus was tied off, and the lung was immersed in a large volume of 10% buffered formalin. After complete fixation (>1 week), the lungs were removed, 10 random samples were harvested, and tissues were submitted for paraffin embedding and hematoxylin and eosin staining. Mean linear intercept for each animal was determined from measures on 4 randomly chosen fields of 4 slides from each animal. A healthy animal lung, prepared and analyzed in identical fashion, was used to provide normal reference control values.

Table 2. Physiologic and radiological characterization of emphysema model

Time point	TLC liters	RV liters	D_{Lco} ml/min/mm Hg	D_L/V_A mm Hg/min	CT density (HU)
BL	3.78 ± 0.47	0.40 ± 0.26	18.2 ± 3.7	5.59 ± 0.49	−712 ± 40
EMPH	4.06 ± 0.66	0.64 ± 0.28	11.6 ± 2.2	3.78 ± 0.83	−796 ± 27
p value*	0.07	0.03	0.0003	0.0014	0.006

* Comparisons performed by paired t test.

Table 3. Mean linear intercept of healthy and experimental emphysema lung tissue

Group	Mean linear intercept	Mean % increase from healthy lung	p value ANOVA vs. normal lung
Healthy lung	59.9 ± 11.4	–	–
Sham treatment	91.6 ± 15.0	53	0.017
BLVR	86.8 ± 10.3	45	0.026
LVRS	88.8 ± 15.4	48	0.024

Table 4. Effects of volume reduction intervention on TLC, RV, and D_{Lco}

	Control	BLVR	LVRS
TLC, liters			
BL	3.72 ± 0.32	3.64 ± 0.42	4.03 ± 0.64
EMPH	3.61 ± 0.35	4.01 ± 0.41*	4.55 ± 0.83*
TX	3.90 ± 0.40	3.84 ± 0.38	3.95 ± 1.07
RV, liters			
BL	0.23 ± 0.31	0.42 ± 0.42	0.57 ± 0.54
EMPH	0.30 ± 0.23	0.52 ± 0.17	1.12 ± 0.52*
TX	0.52 ± 0.30*	0.41 ± 0.11	0.88 ± 0.54
D_{Lco}, ml/min/mm Hg			
BL	19.6 ± 5.3	17.3 ± 3.2	17.7 ± 3.0
EMPH	11.7 ± 1.9*	9.9 ± 2.2*	13.1 ± 1.9*
TX	13.8 ± 2.7*	11.9 ± 1.4*	12.3 ± 2.2*

* Significantly different from baseline value for that test group by ANOVA for repeated measures.

Statistical Analysis

Results for each physiological outcome parameter are described as mean ± standard deviations. Statistical significance was defined as $p < 0.05$. Statistically significant differences between different treatment groups at different time points were assessed by multifactorial ANOVA for repeated measures, in which treatment and time were considered the independent factors. Differences for continuous variables occurring between baseline and EMPH time points were identified by paired t test analysis.

Results

Characterization of Extent of Emphysema in the Papain Model

The papain dosing used in this study produced an experimental model of emphysema that was more severe than the models generated using prior treatment protocols [7, 14]. Physiological (TLC, RV, D_{Lco}, D_L/V_A) and radiographic (chest CT density measurements at 15 cm H_2O transpulmonary distending pressure) parameters used to characterize the extent of disease in the model are summarized in table 2.

Nebulized papain caused a 7.5% increase in TLC, 60% increase in RV, 36% reduction in D_{Lco}, and 12% reduction in CT scan density. These changes confirm hyperinflation and tissue destruction consistent with moderate emphysema.

Stereology (table 3) indicated significant tissue destruction relative to normal lung. Mean linear intercept values for sham control, LVRS, and BLVR animals were significantly larger than those of healthy lung. Representative histology of normal lung, sham treatment, BLVR, and LVRS tissue is shown in figure 1.

Lung Volumes, D_{Lco}, and CT Tissue Density following Volume Reduction Intervention

The effects of sham treatment, LVRS and BLVR on TLC, RV, and D_{Lco} at 3 months are summarized in table 4. Both LVRS and BLVR caused a reduction in lung volume, while volumes in control animals tended to stay the same or increased over time, suggesting worsening emphysema.

D_{Lco} declined relative to baseline at the EMPH in each group, and remained unchanged thereafter.

Lung and Chest Wall Input Impedance following Development of Experimental Emphysema

Papain exposure produced changes in airway resistance (R_{aw}), tissue resistance (G_L), and tissue elastance (H_L) from baseline that were similar to those observed in

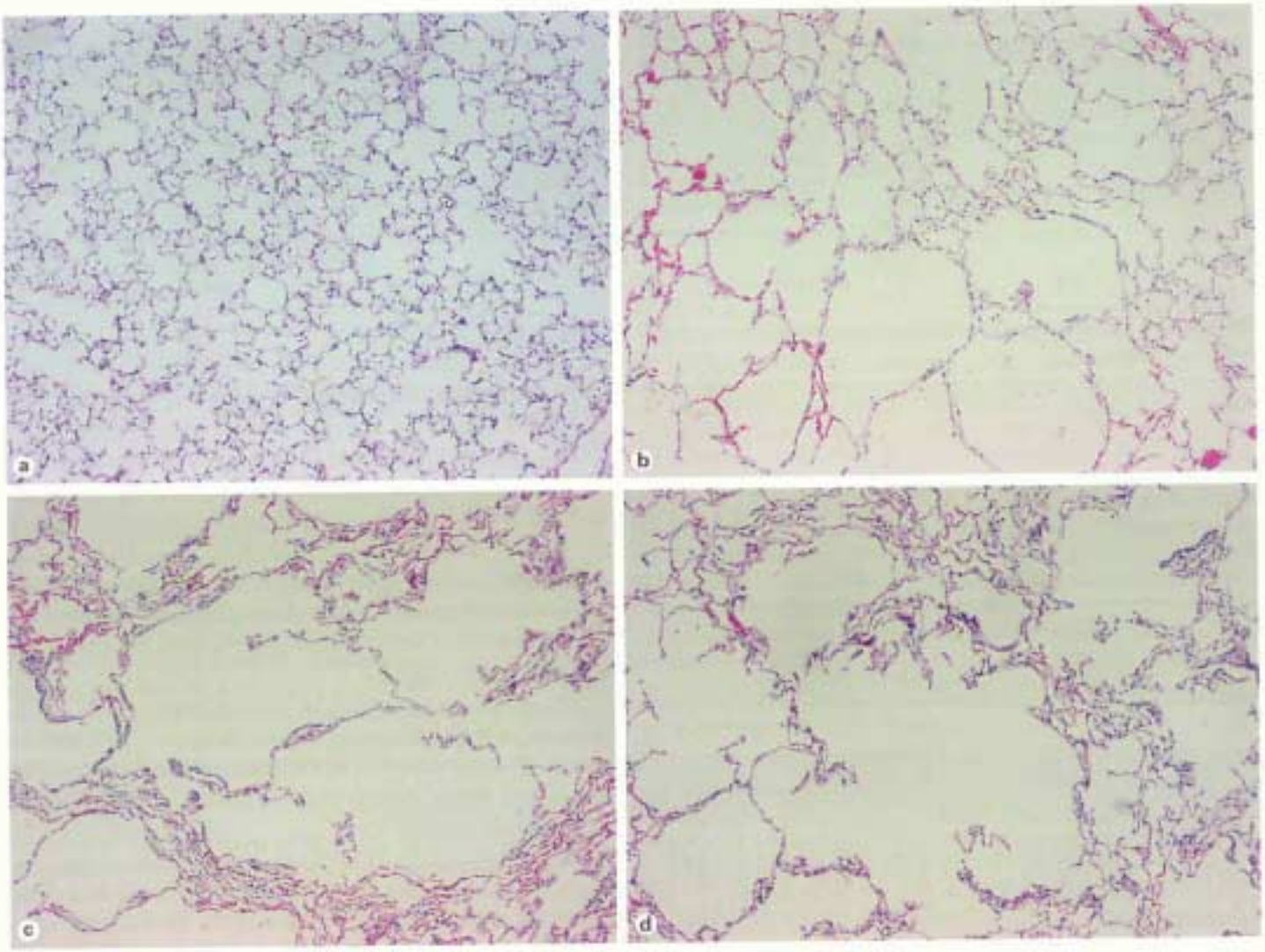


Fig. 1. Representative histopathology from healthy sheep lung (**a**) and damaged areas of sheep lung with experimental emphysema (**b**). Sections from sham-treated, BLVR (**c**), and LVRS (**d**) animals are shown.

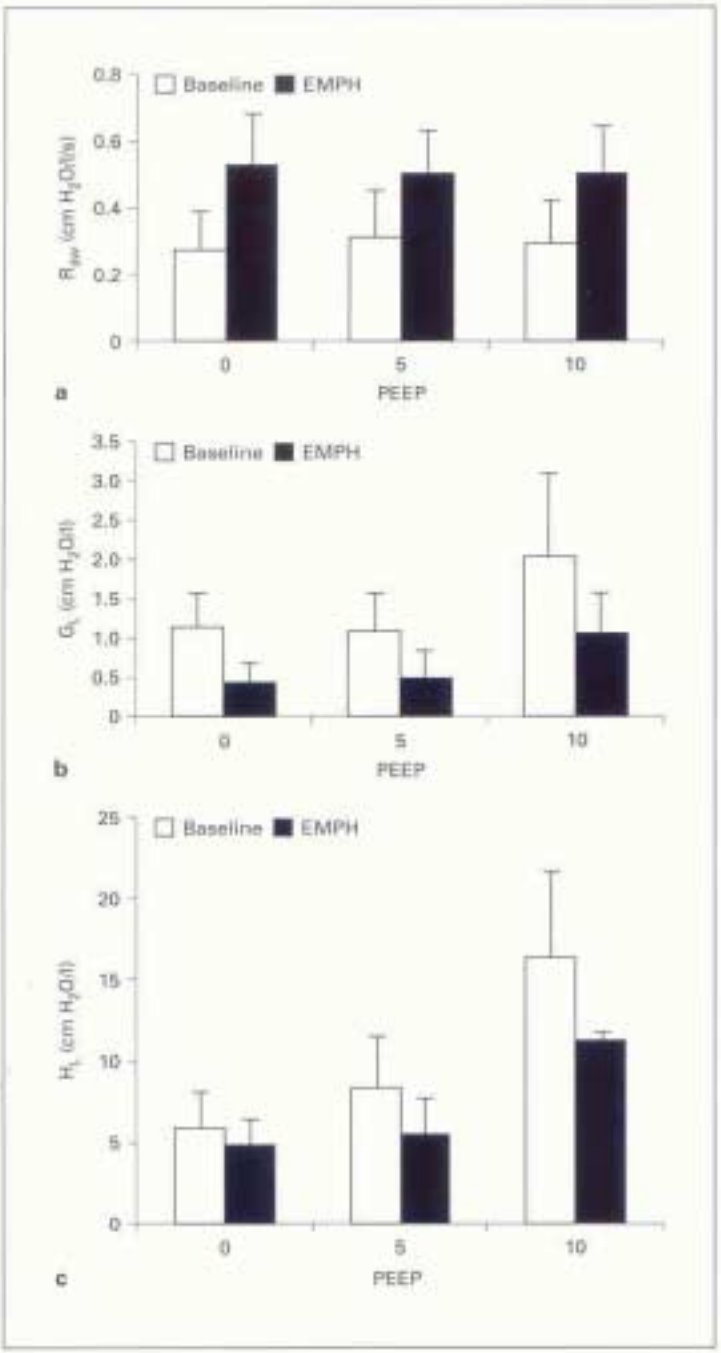
humans with advanced emphysema, and similar to those previously described in animal models of experimental emphysema [1, 14–16]. Airway resistance increased 1.6- to 2.0-fold from baseline at the EMPH time point following papain (fig. 2a). Lung tissue resistance and elastance, expressed as G_L and H_L, both decreased following development of experimental emphysema [14, 17, 18]. Changes from baseline were most evident at 5 and 10 cm H_2O PEEP (fig. 2b, c). Chest wall tissue resistance (G_{CW}) also increased at EMPH compared to baseline (fig. 3b).

At baseline prior to development of emphysema, the relative contributions of lung and chest wall to total respiratory system impedance measured in healthy, anesthetized sheep were similar to those reported in other animals, and in healthy humans (fig. 4) [19–22].

Following development of emphysema, the overall magnitude of respiratory system impedance, equal to $\sqrt{(R_{rs} + G_{rs}/\omega^{\alpha})^2 + (I_{rs}\omega - H_{rs}/\omega^{\alpha})^2}$ was not significantly different from baseline, although specific changes in individual components of impedance were observed:

(1) R_{rs} increased relative to baseline ($p < 0.01$), due to an increase in R_{aw} ($p < 0.001$);

(2) G_{rs} was unchanged relative to baseline (p = NS), as reductions in G_L ($p < 0.001$) were offset by increases in G_{CW} ($p < 0.001$);



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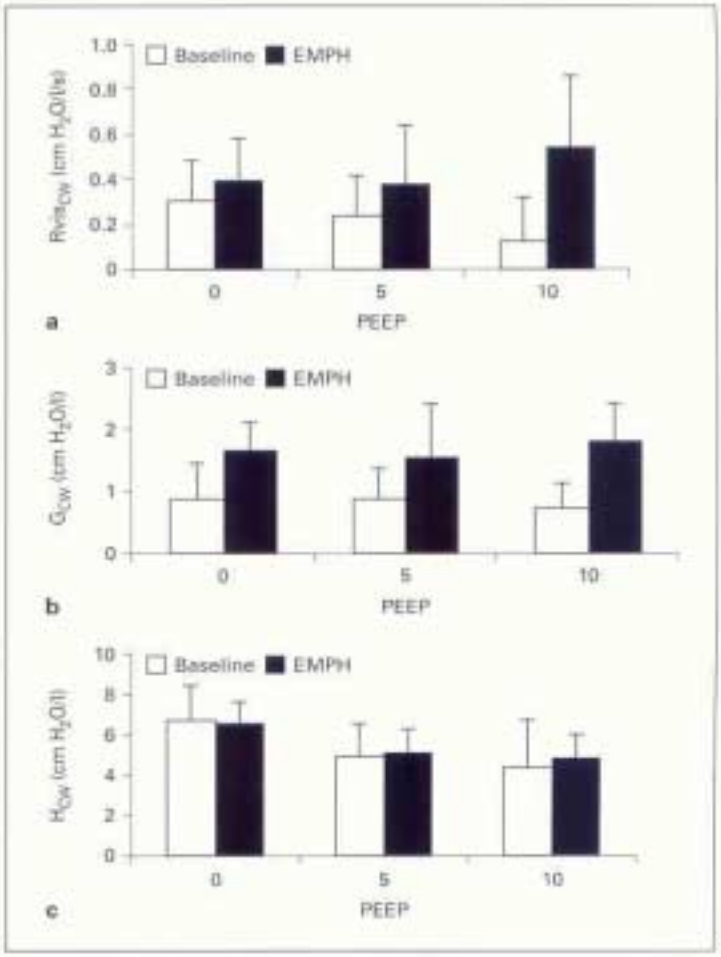

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Fig. 2. Comparison of baseline and post-papain (EMPH) lung impedance parameters for all 12 sheep is presented at 0, 5 and 10 cm H_2O PEEP. At the EMPH time point, airway resistance (R_{aw}) (**a**) increased significantly, and tissue resistance (G_L) (**b**) and elastance (H_L) (**c**) decreased significantly at all PEEP levels.

Fig. 3. Comparison of baseline and post-papain (EMPH) chest wall impedance parameters for all 12 sheep is presented at 0, 5 and 10 cm H_2O PEEP. At the EMPH time point, chest wall Newtonian resistance ($Rvis_{CW}$, analogous to R_{aw} in the lung) (**a**) tended to increase, but this was not statistically significant. Chest wall tissue resistance (G_{CW}) (**b**) increased significantly following papain exposure ($p < 0.05$; two-way ANOVA for repeated measures). Chest wall elastance (H_{CW}) (**c**) did not change.

(3) H_{rs} was reduced relative to baseline ($p = 0.18$, NS) as H_L decreased ($p = 0.02$) following papain treatment, while H_{CW} was unchanged (p = NS).

Effect of BLVR and LVRS Treatment on Lung and Chest Wall Impedance

Responses to sham treatment, BLVR, and LVRS in experimental emphysema are summarized in figures 5a–f. Following sham treatment, changes in respiratory system impedance consistent with progression of emphysema were observed. Airway resistance trended upward and lung tissue resistance and elastance downward, although values at the 3-month follow-up time point were not significantly different from those measured at the time of treatment (i.e. EMPH).

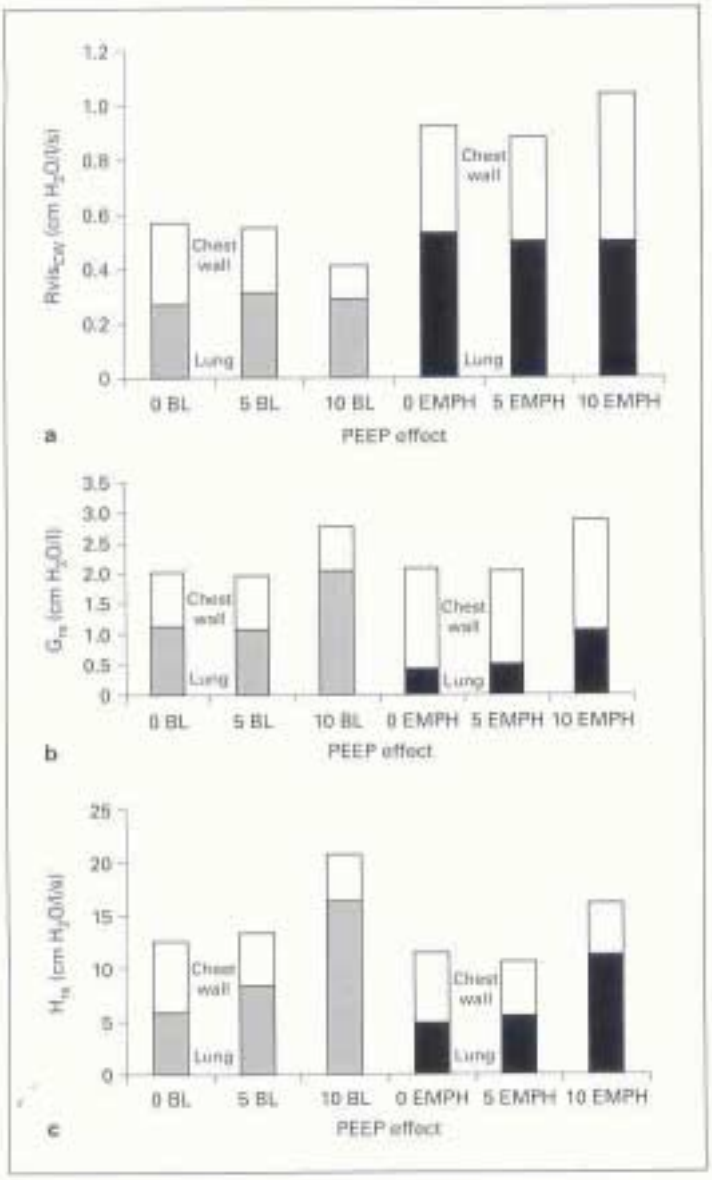

Fig. 4. Stacked bar chart showing the relative contributions of chest wall and lung to total respiratory system impedance components at baseline (BL) and following development of experimental emphysema (EMPH). Chest wall Newtonian resistance ($Rvis_{CW}$) contributed about 40–45% of frequency-independent resistance at baseline, and airway resistance (R_{aw}) the remainder, with no PEEP effect (**a**). The chest wall contribution to both frequency. **a** Distribution of $Rvis_{CW}$ between lung and chest wall. **b**, **c** Lung and chest wall contributions of G_{rs} (**b**) and H_{rs} (**c**) as a function of PEEP.

Following BLVR, airway resistance continued to increase, and lung tissue resistance continued to decrease, in a manner similar to that observed in sham-treated animals. Lung elastance, which continued to decline in control animals at all levels of PEEP, increased at higher PEEP levels following BLVR treatment, although the increase was not statistically significant.

Following LVRS, airway resistance increased, and lung tissue resistance decreased in a manner similar to control and BLVR treatment groups. Lung elastance showed PEEP-dependent increases post LVRS similar to those in BLVR treatment animals. Despite having undergone a thoracotomy, animals treated with LVRS did not demonstrate any increases in chest wall impedance.

Necropsy Findings – Pleural Scarring Reactions in Control, BLVR, and LVRS Animals

Necropsy findings in sham-treated emphysema animals revealed grossly normal-appearing lungs in 2 animals, and 2 small 'blebs' on the lung surface of the remaining 2 animals. There were no pleural space adhesions, and no other visceral or parietal pleural lesions noted.

Three of four BLVR-treated animals demonstrated infolding on the visceral pleural surface and underlying parenchymal scarring at the sites of BLVR treatment throughout the lungs, consistent with previously reported findings [4]. There were no pleural space adhesions, and no other visceral pleural lesions noted.

All animals treated with LVRS demonstrated extensive pleural scarring (fig. 6). In 2 animals, where surgical treatment involved more caudal locations, adhesions directly involved the thoracic surface of the costal portion of the diaphragm.

Discussion

The present study, performed in sheep with experimental emphysema, compares lung and chest wall input impedance measurements at normal breathing frequencies following volume reduction therapy performed via either a nonsurgical, endobronchial approach or a standard open surgical approach. Based upon prior observations and reports, it was hypothesized that changes in lung impedance following the two volume reduction treatments would be nearly equivalent, while chest wall impedance would be higher in animals treated with the open surgical approach due to pleural scarring and chest wall distortion [7, 23]. It was further postulated that an increase in chest wall impedance would adversely affect responses to surgical lung volume reduction by imposing a restrictive physiological deficit that was not present preoperatively. This would tend to increase respiratory system work of breathing, partially negating the benefits associated with lung volume reduction.

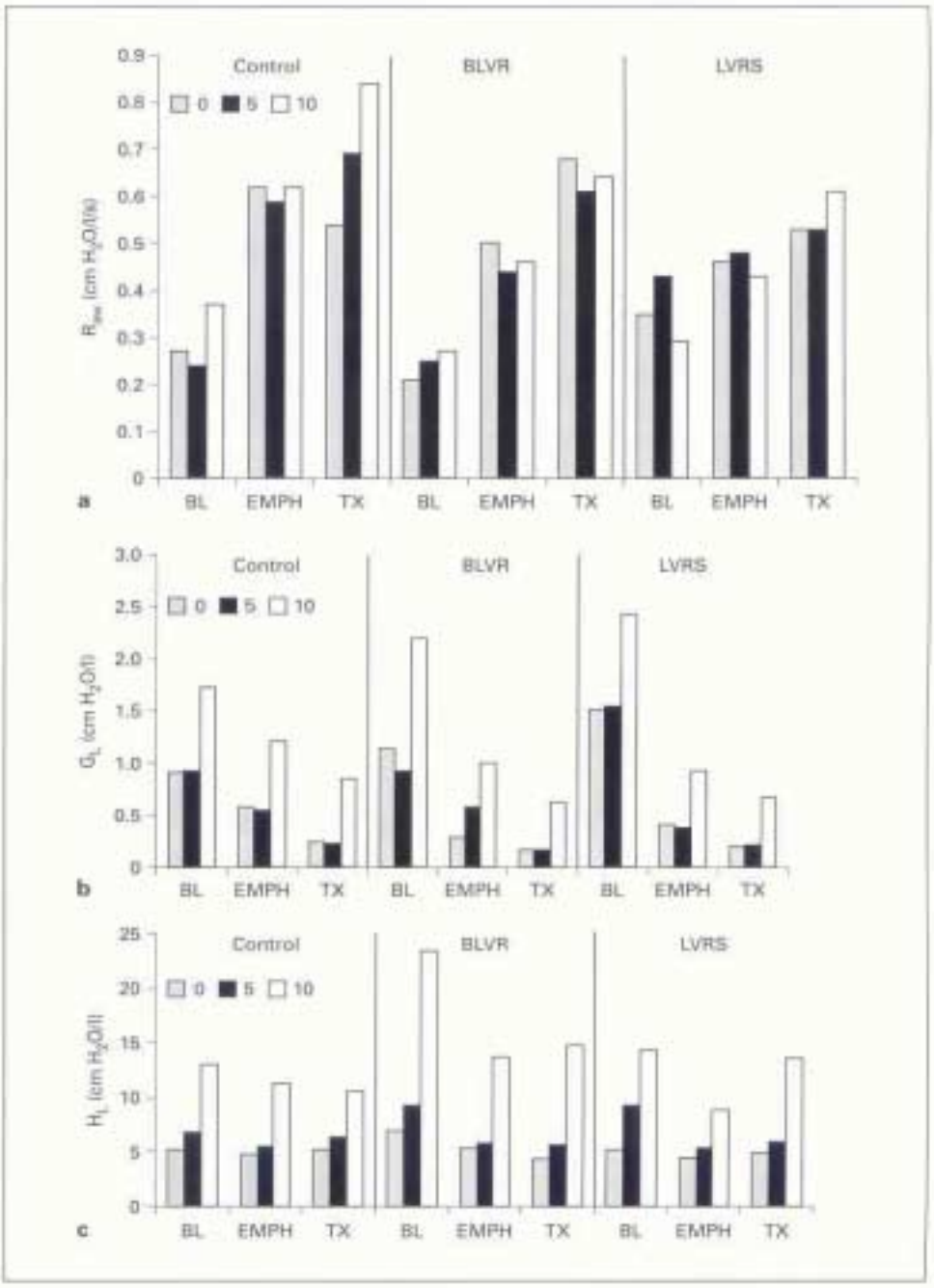

Fig. 5. Treatment responses for control, BLVR, and LVRS animals as a function of PEEP. Airway resistance (R_{aw}) increased significantly from baseline (BL) to post-papain (EMPH), and from post-papain to 3-month post-treatment (TX) in all groups. Lung tissue resistance (G_L) decreased significantly from BL to EMPH, and from EMPH to TX in all treatment groups. Lung elastance (H_L) decreased from BL to EMPH in all groups. In control animals, H_L tended to decrease further at higher levels of PEEP from EMPH to TX, while BLVR and LVRS animals demonstrated the opposite tendency, presumably in response to treatment. $Rvis_{CW}$ and H_{CW} did not change in any consistent manner throughout the course of the study. G_{CW}, however, increased significantly from BL to EMPH, and decreased from EMPH to TX time points in all treatment groups. **a** R_{aw} post treatment. **b** G_L post treatment. **c** H_L post treatment.

(For figure 5d–f see next page.)

Since both surgical and nonsurgical approaches to volume reduction will likely be available soon for clinical use, defining physiological differences in response to these two approaches may be important in assisting clinicians with procedural selection. By not adversely affecting chest wall impedance, endobronchial lung volume reduction could, in theory, confer greater physiological benefit than surgical lung volume reduction for an equivalent reduction in lung volume.

Serial measurements of respiratory system input impedance before and after BLVR and LVRS have not been possible in humans. Therefore, an experimental model of emphysema was used in which detailed physiological measurements and imaging studies, similar to those com-

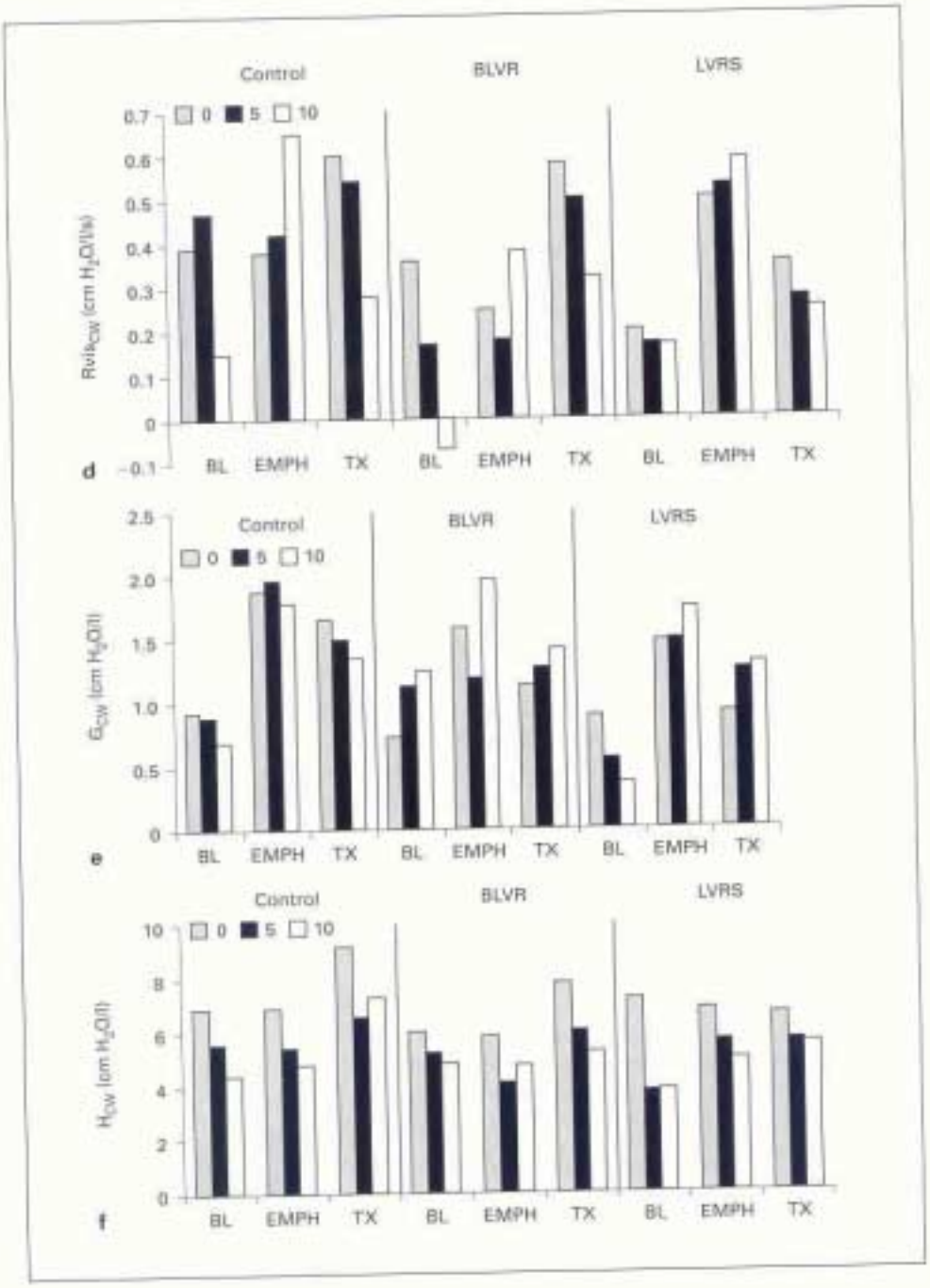

Fig. 5. **d** $Rvis_{CW}$ post treatment. **e** G_{CW} post treatment. **f** H_{CW} post treatment.

monly used in clinical practice, were measured to characterize the model and assess responses to treatment. Measurements indicate that the experimental sheep model employed here represents moderately advanced, homogeneous emphysema. The model, resulting from long-term high dose exposure to nebulized papain (total dose of 900 U/kg over 10 weeks), possesses histological, radiographic, and physiological features of emphysema observed in human patients [1, 14, 24, 25]. In assessing the relevance of the observation described in this study to clinical medicine, it is important to recognize that, despite showing significant physiological changes from baseline, the emphysema in this sheep model is not as severe as in patients who are presently considered candi-

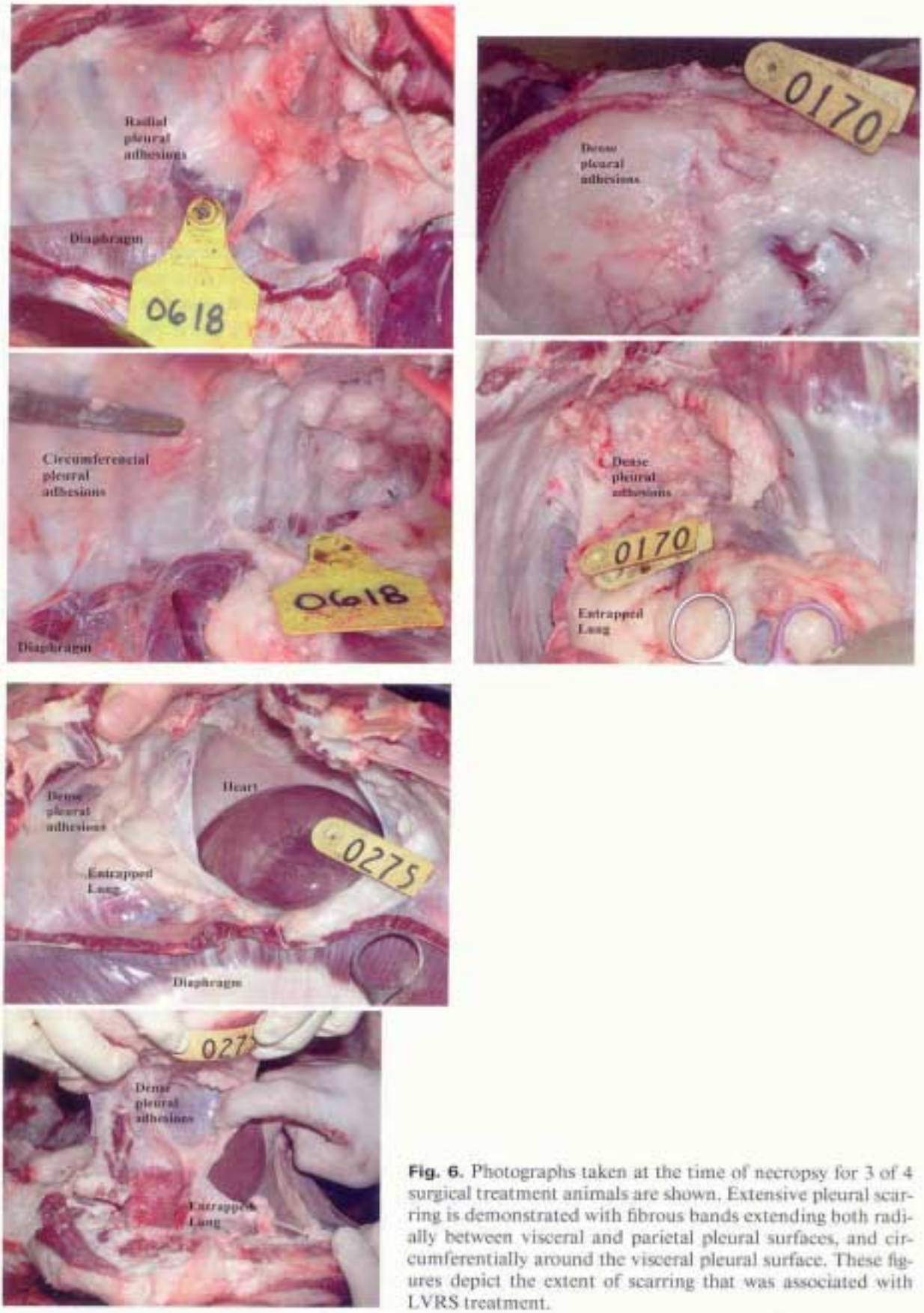

Fig. 6. Photographs taken at the time of necropsy for 3 of 4 surgical treatment animals are shown. Extensive pleural scarring is demonstrated with fibrous bands extending both radially between visceral and parietal pleural surfaces, and circumferentially around the visceral pleural surface. These figures depict the extent of scarring that was associated with LVRS treatment.

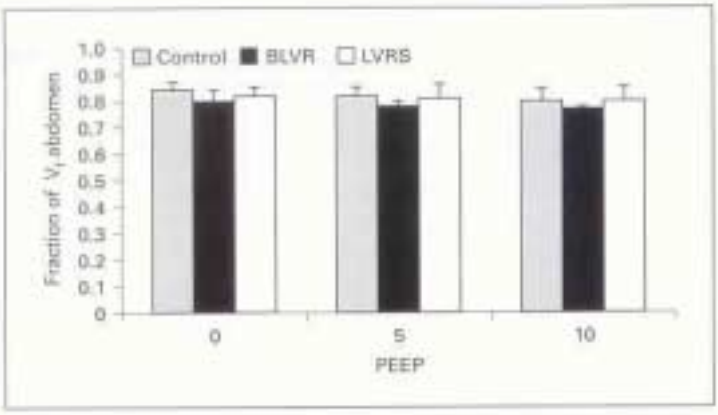

Fig. 7. Respitrace partitioning – abdominal and chest wall motion. The fraction of total chest wall movement contributed by abdominal motion is shown for each treatment group. Tidal volumes were identical to those used during OVW measurements (0.5 liter). In each treatment group and for each test condition, positive pressure ventilation produced tidal breathing in which the majority of chest wall excursion motion was abdominal.

dates for volume reduction therapy. Furthermore, disease in this experimental model is more homogeneous than in the majority of patients referred for LVRS. Thus, changes in lung mechanics following either BLVR or LVRS treatment are not likely to be the same as those observed in patients. Nevertheless, the pattern of change reported here is likely to be similar to that anticipated in humans, and allows assessment of the differential effects of BLVR and LVRS on lung and chest wall impedance.

In the present study, coincident with the development of emphysema, chest wall tissue resistance increased. This change, while statistically significant, was small in relation to the magnitude of total respiratory system impedance, which is equal to $\sqrt{Re[Z_{rs}]^2 + Im[Z_{rs}]^2}$. Thus, it is not expected to have physiological consequences during normal breathing.

Following intervention, impedance values differed among the three test groups. In sham-treated animals, the physiological changes of emphysema progressed spontaneously over time out to 3 months in the absence of further papain treatments. Airway resistance continued to increase, lung tissue resistance and elastance continued to decrease, and chest wall parameters remained unchanged from pretreatment emphysema values. At 3 months following treatment, both BLVR and LVRS were associated with changes in lung elastance indicative of volume reduction therapy. At PEEP levels representative of normal breathing (0–5 cm H_2O), lung elastance was unchanged from EMPH values, while at higher levels of PEEP (10 cm H_2O), increases in elastance were observed in BLVR and LVRS groups relative to pretreatment values ($p < 0.05$ by paired analysis for both groups relative to 0 PEEP values), consistent with changes in static elastic recoil that have been reported following volume reduction therapy in humans [26].

Neither BLVR nor LVRS treatment altered the time course of change in airway or lung tissue resistance compared to that observed in sham-treated animals, however. Airway resistance continued to increase, and lung tissue resistance continued to decline, following both forms of volume reduction therapy.

Necropsy findings (fig. 6) demonstrated extensive pleural scarring in LVRS-treated animals. Despite this, there were no differences in chest wall impedance values among the three treatment groups at the 3-month follow-up. At necropsy in LVRS animals, pleural scarring with fibrous tissue extending circumferential around the visceral pleura, and radially between the visceral and parietal pleura was observed over large portions of the pleural surface. However, these anatomical changes had no physiological effects. Lack of complete pleural symphysis and failure of the adhesions to completely involve the hemithorax may, in part, have accounted for this. However, the primary reason for the lack of a physiological effect appears to relate to tidal breath partitioning between rib cage and diaphragm motion during positive pressure respiration. It was observed that during recordings of input impedance, rib cage excursion was small in relation to diaphragm motion. To further evaluate the partitioning of chest wall motion between rib cage and abdomen during positive pressure ventilation, Respitrace recordings were performed during passive ventilation applying tidal volumes and PEEP levels identical to those used during input impedance measurements performed via the OVW technique. These additional studies, summarized in figure 7, confirm that during positive pressure ventilation, approximately 80% of chest wall motion at PEEP levels between 0 and 10 cm H_2O is diaphragmatic (i.e. abdominal) in all three treatment groups, with only 20% of the motion resulting from rib cage expansion. These data explain why surgical treatment had minimal effects on chest wall impedance despite causing impressive scarring of the upper thoracic pleural surface. Because rib cage motion during positive pressure ventilation is small relative to diaphragmatic excursion, 'chest wall' impedance measured in this study predominantly reflects impedance associated with abdominal rather than rib cage motion. Diaphragmatic breathing is likely to occur in patients fol-

lowing LVRS as well, suggesting that, except in those instances where pleural scarring directly impedes diaphragm motion, as might occur following LVRS treatment of lower lobe disease, the pleural scarring associated with LVRS is not likely to be physiologically significant.

In conclusion, the present study confirms previous observations regarding the effects of LVRS and BLVR on lung mechanics, and provides new information concerning how the two treatments affect dynamic respiratory system impedance at physiologically relevant breathing frequencies and PEEP levels. The results demonstrate that 10 weeks of papain in sheep produces experimental emphysema of moderate severity in which 50–60% increases in mean linear intercept are associated with significant gas trapping and reductions in diffusing capacity. Physiological changes following treatment with nebulized papain progress over time even in the absence of continued papain treatments. Both LVRS and BLVR produced PEEP-dependent increases in lung recoil, but had no effect on airway or tissue resistance values. Despite causing extensive pleural scar formation, LVRS had no adverse effects on chest wall or overall respiratory system impedance when compared to BLVR.

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