GENERAL THORACIC SURGERY

LUNG VOLUME REDUCTION SURGERY RESTORES THE NORMAL DIAPHRAGMATIC LENGTH-TENSION RELATIONSHIP IN EMPHYSEMATOUS RATS

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Objective: Improved respiratory muscle function is a major effect of a lung volume reduction surgery. We studied length adaptation in rat diaphragmatic muscle in an attempt to elucidate the mechanism by which diaphragmatic function improves after this controversial operation.

Methods: We developed a model of elastase-induced emphysema and bilateral volume reduction through median sternotomy in rats. Five months after emphysema induction, maximum exchangeable lung volume was determined in intubated and anesthetized control animals and animals with emphysema. Costal diaphragmatic length was measured in vivo, and the length at which maximal twitch force is generated was determined on muscle strips in vitro. Also 5 months after elastase administration, another cohort underwent volume reduction or sham sternotomy. Five months after the operation, these animals were similarly studied.

Results: Lung volume was increased in emphysematous rats versus control rats (50.9 ± 1.7 vs 45.4 ± 1.3 mL, $P = .001$). Lung volume was decreased in emphysematous animals that had undergone volume reduction versus sham sternotomy (44.7 ± 0.60 vs 49.4 ± 1.0 mL, $P = .001$). In situ diaphragm length (1.99 ± 0.04 vs 2.24 ± 0.07 cm, $P = .001$) and the length at which maximal twitch force is generated (2.25 ± 0.06 vs 2.48 ± 0.09 cm, $P = .038$) were shorter in emphysematous than control animals. After volume reduction, in situ diaphragm length (2.13 ± 0.06 vs 1.83 ± 0.02 cm, $P < .001$) and the length at which maximal twitch force is generated (2.50 ± 0.08 vs 2.27 ± 0.06 cm, $P = .013$) were longer than in animals undergoing sham sternotomy.

Conclusions: In this experimental model of emphysema and lung volume reduction surgery, emphysema shortens the length at which maximal twitch force is generated and shifts the diaphragmatic length-tension curve to lower lengths; volume reduction returns the length at which maximal twitch force is generated toward normal and shifts the diaphragmatic length-tension curve back to longer lengths. This restoration toward normal physiology may enable the improvement in diaphragmatic function seen after lung volume reduction surgery. The mechanism by which these length adaptations occur merits further investigation. (J Thorac Cardiovasc Surg 2001;121:217-24)

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Lung volume reduction surgery (LVRS) has recently regained popularity as a treatment for patients with severe emphysema.[1,2] Two major physiologic mechanisms have been proposed that may underlie the improvements in pulmonary function and dyspnea which have been demonstrated to occur in properly selected patients after LVRS. These mechanisms are (1) changes in the elastic recoil of the lung itself and (2) improvements in respiratory muscle function. Although most research has focused on the first of these mechanisms, there are several studies that have documented improvements in diaphragmatic function after LVRS in human subjects.[3-6] To date, there have been no studies in experimental animals examining this issue of respiratory muscle function after LVRS.

By means of the well-established model of elastase-induced emphysema in rodents, it has been established that diaphragmatic muscle fibers shorten as the muscle is pushed caudad by the hyperexpanded, emphysematous lung. Accompanying this shortening in fiber length is a corresponding decrease in the length of the fibers at which peak contractile force is attained (Lo).[7,8] This Lo adaptation is thought to maintain the diaphragm at close to the optimal point on its length-tension curve, thus ameliorating the loss of diaphragmatic function that results from the displaced muscle being in a mechanically disadvantaged position.

One study has suggested that improvements in diaphragmatic function after LVRS do not reach statistical significance until 6 months after the procedure.[9] This finding is consistent with our concept of the likely interactions between lung volume and diaphragmatic mechanics after LVRS. Acutely elevating the diaphragm in a craniad direction by removing emphysematous lung tissue would be expected to stretch diaphragmatic fibers beyond their Lo (a Lo that has been reduced as an adaptation to chronic emphysema). This state of diaphragmatic overstretch might actually decrease diaphragmatic contractility acutely after LVRS. Only if diaphragmatic muscle fibers can adapt after the procedure by increasing Lo (an adaptation that would likely require months) could the full benefit of the elevated, more physiologically positioned diaphragm be realized.

We therefore set out to test the hypothesis that the diaphragm adapts after LVRS in the emphysema rat model not only by increasing the length of its fibers but also by increasing the Lo of those fibers. Such an adaptation would return the diaphragm toward its optimal operating range on its length-tension curve, thus enabling postoperative improvement in diaphragmatic function.

Methods

Emphysema induction. Emphysema was induced in 3-month-old Sprague-Dawley rats by means of a single intratracheal instillation of porcine pancreatic elastase (ICN Biochemicals, Cleveland, Ohio), 25 U/100 g body weight, diluted in 0.60 mL of normal saline solution. The animals were anesthetized with inhaled isoflurane and endotracheally intubated with a nonocclusive, 16-gauge, 5.25-inch intravenous catheter (Angiocath; Becton Dickinson, Sandy, Utah). The elastase solution was introduced slowly while rotating the animals to achieve uniform distribution to each lung. Three positive pressure breaths (peak pressure, 25 cm H_2O) were then administered to move the solution into the most distal airways. With this procedure, approximately 20% of the animals died of pulmonary hemorrhage within 1 hour of the instillation. The surviving animals were returned to the animal care facility and managed routinely until 5 months after induction. Control animals underwent an identical procedure with 0.60 mL of normal saline solution without elastase.

In all subsequent analyses the investigator performing the measurements was blinded to whether the animal being studied represented an animal with emphysema, a control animal, or an LVRS animal.

Technique of lung volume reduction. Lung volume reduction was performed on a cohort of rats with emphysema 5 months after emphysema induction. The animals were anesthetized and intubated with a nonocclusive catheter, as above. Their lungs were ventilated with a Rodent Ventilator (CWE Inc, Ardmore, Pa) by using 100% oxygen at 90 breaths/min, with flows adjusted to keep peak inspiratory pressures below 15 cm H_2O. The animals were shaved, prepared, and draped in a supine position, with the upper extremities held inferiorly by nonconstricting wrist straps. A median sternotomy was performed. The internal thoracic vessels were ligated bilaterally after division of the upper 2 cm of sternum to prevent subsequent bleeding from these vessels, resulting from their proximity to the narrow rat sternum. The pleurae were entered bilaterally. The upper lobe on the right and the upper one third of the left lung were resected after clamping, and the stumps were ligated with 3-0 polyglycolic acid ties. Ventilation was transiently held while the ties were secured. A single**,** 16-gauge, 1.88-inch intravenous catheter was placed into each hemithorax through separate intercostal stab incisions and placed to –2 cm H_2O suction. The sternum was closed with running 3-0 polypropylene sutures, the presternal muscle layer with running 3-0 polyglycolic acid ties, and the skin with running 4-0 polyglycolic acid ties.

The animals were awakened and extubated. In no animal was there a persistent air leak after the cessation of positive-pressure ventilation, and the chest tubes were removed when the animals began to attempt to ambulate (3-5 minutes after extubation).

Sham sternotomy was performed on another cohort of animals with emphysema 5 months after induction in precisely the same manner as the LVRS described above, including the opening of the pleurae and the placement of chest tubes, but without the pulmonary resection.

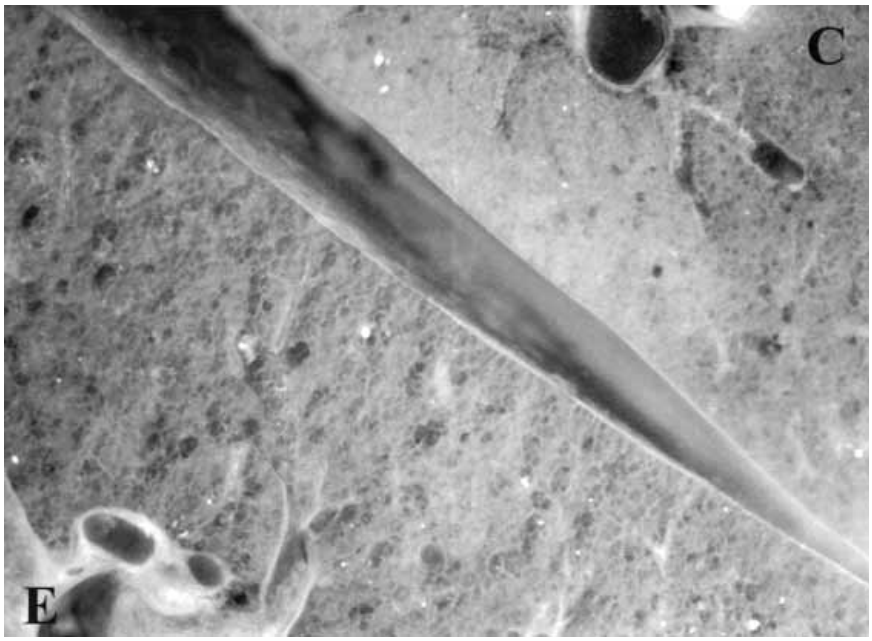

Fig 1. Magnified view (10×) of emphysematous *(E)* and control *(C)* lung showing the characteristic changes of elastase-induced emphysema (see text for method of preparation).

Lung volume determination. Five months after induction of emphysema and 5 months after LVRS or sham sternotomy, maximum exchangeable lung volume (MELV) was determined on control animals and animals with emphysema as follows (before death for the in vitro muscle study described below). The animals were anesthetized and intubated with a 16-gauge, 5.25-inch intravenous catheter modified with an umbrella-shaped latex cuff that provided an occlusive endotracheal tube, allowing no air leakage around the tube. Anesthesia was deepened to apnea. The supine rats were taken off of the ventilator, and a 60-mL syringe was attached to a 3-way stopcock with one arm to the endotracheal tube and the third arm to a water manometer (10AA25; Meriam Instruments, Cleveland, Ohio). The lungs were inflated to 25 mL above functional residual capacity 3 times to standardize preinflation volumes and were then allowed to return to functional residual capacity. Using, as an approximation, the finding of Koo and colleagues[10] that total lung capacity in rodents represents that volume exchanged between –25 and +25 cm H_2O transpulmonary pressure, we then inflated the lungs stepwise by the volume required to achieve stable pressures of 5, 10, 15, 20, and 25 cm H_2O. This was followed by withdrawing volumes required to achieve stable pressures of –5, –10, –15, –20, and –25 cm H_2O. The volumes at each pressure were recorded. The MELV, a measure of compliance, represents the total volume exchanged between –25 and +25 cm H_2O pressure. We made no effort to measure changes in expiratory air flows because it is lung volumes, not air flows, that are critical to diaphragm length adaptation, the focus of this study.

Measurement of in situ diaphragm fiber length. Control rats and rats with emphysema 5 months after induction and LVRS and sham sternotomy rats 5 months after the operation underwent the following studies after determination of their MELV. Rats were killed by carbon dioxide inhalation and immediately underwent laparotomy. The pleural space was specifically left unbreached to maintain the normal negative intrathoracic pressure and thus as close to the physiologic diaphragmatic geometry as possible. A soft curved 0.5-mm scale was gently applied to the abdominal surface of the diaphragm without disturbing the muscle's natural position, and the length of the fibers from central tendon to costal insertion was measured. This measurement was taken on the right hemidiaphragm at a reproducible point 0.5 cm anterior to the phrenic nerve insertion.

Determination of Lo. An apparatus for the in vitro study of muscle contractile characteristics similar to that described previously[11] was assembled. After measurement of in situ diaphragm fiber length, as described above, the diaphragm was quickly removed en bloc with the rib cage intact circumferentially, and it was placed in oxygenated Ringer's solution buffered to pH 7.4 with 10 mmol/L N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid. One muscle strip 7.5 mm in width, extending from and including the central tendon and rib attachments, was carefully dissected out under a dissecting microscope. The strip was centered on the identical location in the right hemidiaphragm where the in situ length measurement had been obtained. Care was taken to dissect parallel to the muscle fibers, creating a slightly tapered strip.

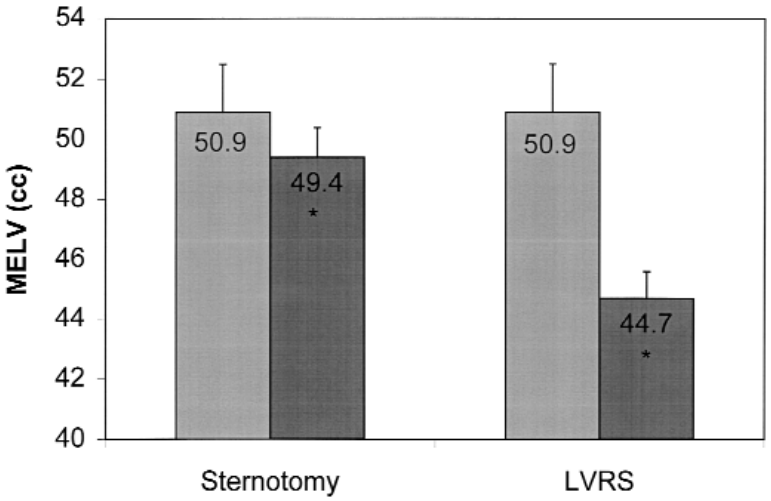

Fig 2. Preoperative *(light gray)* and postoperative *(dark gray)* MELVs in animals with emphysema undergoing LVRS and sham sternotomy. The MELVs did not change significantly after sternotomy but significantly decreased after LVRS. *Asterisks* denote statistical significance between those values so identified ($P = .001$). Values are means ± SE.

Each strip was mounted horizontally in a bath of continuously circulating oxygenated solution at 23°C ± 1°C. One end of the strip was tied to a fixed post with two 3-0 silk sutures taken through the attached ribs. The central tendon at the other end was affixed to the arm of a servomotor system (motor model 6450, electronics model 300B; Cambridge Technology, Watertown, Mass) on a movable platform with a single 4-0 silk tie. Platinum electrodes (each 7 × 25 mm) were placed within 1 mm of the muscle strip on either side. The muscles were stimulated with a Grass S44 stimulator (Grass Instruments, Quincy, Mass) with pulses 1.5 times above those needed to achieve maximal twitch force (70 V, 5 ms pulses). A series of twitches generated every 5 seconds at incrementally different muscle lengths was used to identify the Lo. This length was then measured along the middle of the strip, from tendon insertion to costal insertion, by means of calipers.

A length-tension curve was generated by using 5 twitches at each muscle length between 70% and 120% of the previously determined Lo. All data presented represent the mean of these 5 twitches. Muscle length (using the servomotor), stimulator pulse timing, and data collection were under computer control by means of custom software developed in our laboratory. A Pentium computer with data acquisition board (DT21-EZ, Data Translation, Marlboro, Mass) controlled the experiment and recorded all data to disk for later analysis.

After study, the strip was removed from the apparatus, trimmed of nonmuscle tissue, blotted dry, and weighed. The total muscle strip cross-sectional area was calculated as wet muscle mass divided by muscle length times density, with a value of 1.06 g/cm^3 being used for muscle density.[12] Analysis of the data used custom software that picked the developed force per twitch and averaged this value for each series of twitches at the same length. Tension was calculated by dividing developed force by the calculated cross-sectional area.

The use of laboratory animals in this protocol was approved by the animal care committees of the University of Pennsylvania and the Philadelphia Veterans Affairs Medical Center. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animals Resources, National Research Council, and published by the National Academy Press (revised 1996).

Results

Documentation of emphysema. Fig 1 shows thickly sectioned emphysematous and control lung photographed side-by-side under 10× magnification. These representative specimens are taken from the same portion of the right middle lobe of each animal 5 months after administration of elastase or saline solution. The explanted lungs were distended with formalin infused through the trachea at 20 cm H_2O and then fixed overnight. The photographs document the enlarged air spaces and disrupted alveolar walls characteristic of elastase-induced emphysema.[13] These changes were present throughout the lung parenchyma, but the severity varied, with a patchy distribution. Because studies of the time course of the physiologic changes in elastase-induced emphysema have demonstrated that these changes plateau no later than 26 weeks after induction,[14] we chose 5 months as the time point at which to study the animals or perform LVRS or sham sternotomy.

MELV was determined to have a single value that could be used to compare groups of animals with respect to their compliance and lung volume. As

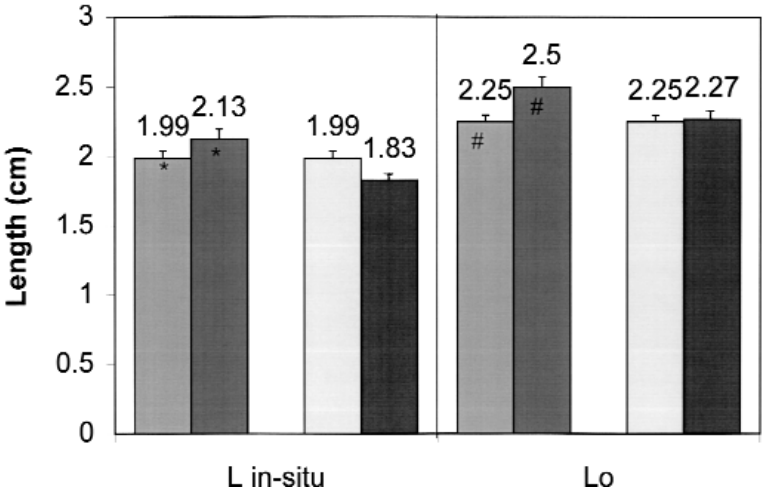

Fig 3. Diaphragm lengths before LVRS *(light gray)*, after LVRS *(dark gray)*, before sternotomy *(white)*, and after sternotomy *(black)*. Both in situ length and Lo increased significantly after LVRS but failed to change significantly after sham sternotomy (*P = .029; #P < .001). Values are means ± SE.

expected, the MELV was significantly increased in emphysematous rats (n = 8) versus control rats (n = 8; 50.9 ± 1.7 vs 45.4 ± 1.3 mL; P = .001 [mean ± SE]).

Documentation of reduction in volume with LVRS. Fig 2 demonstrates that the MELV was significantly decreased in emphysematous animals that had undergone LVRS (n = 11) versus those that had undergone sham sternotomy (n = 7; 44.7 ± 0.60 vs 49.4 ± 1.0 mL; P = .001), documenting that the LVRS procedure successfully reduced lung volume. Also shown in Fig 2 is the fact that there was no significant difference between the mean MELV of unoperated animals with emphysema and animals with emphysema that had undergone sham sternotomy. There was also no significant difference in either the mean weights or the mean head-to-tail lengths of any of the groups of animals that might account for the changes in lung volumes.

In situ length and Lo adaptation. We confirm the finding of others[7,8] that both in situ diaphragmatic length and Lo decrease in response to elastase-induced emphysema. We found in situ length to be 2.24 ± 0.11 cm in 8-month-old control rats and 1.99 ± 0.04 cm in age-matched animals with emphysema (P = .001). Similarly, Lo was 2.48 ± 0.09 cm in control rats and 2.25 ± 0.06 cm in rats with emphysema (P = .038).

Fig 3 shows the effects of LVRS and sham sternotomy on these lengths in animals with emphysema. Sternotomy alone (n = 7) caused no significant changes in either in situ length (1.99 ± 0.04 to 1.83 ± 0.02 cm, P = .35) or Lo (2.25 ± 0.06 to 2.27 ± 0.06 cm, P = .36) 5 months after the procedure. Note that the in situ length actually decreased after sham sternotomy. The lung volume reduction procedure (n = 11), on the other hand, caused significant increases in both in situ length (1.99 ± 0.04 to 2.13 ± 0.06 cm, P = .029) and Lo (2.25 ± 0.06 to 2.50 ± 0.08 cm, P < .001) at 5 months. Looked at another way, 5 months after LVRS both in situ length (2.13 ± 0.06 vs 1.83 ± 0.02 cm, P < .001) and Lo (2.50 ± 0.08 vs 2.27 ± 0.06 cm, P = .013) were longer than in animals undergoing sham sternotomy.

Fig 4 highlights the finding that Lo, which was decreased after the induction of emphysema, returned to nearly exactly the pre-emphysema length after LVRS. In the animals undergoing sham sternotomy, however, Lo failed to significantly change postoperatively.

Fig 5 represents the diaphragmatic length-tension curves in control animals, age-matched animals with emphysema, and animals with emphysema after LVRS. It can be seen that 5 months after the induction of emphysema, the length-tension curve has shifted to the left. Five months after LVRS, the curve has shifted back to the right, such that the post-LVRS diaphragmatic length-tension curve closely matches the normal nonemphysematous animals' length-tension curve. It can also be seen on these curves that there is a trend toward lower peak twitch tension generated by the diaphragmatic strips from animals with emphysema than by the control diaphragmatic strips (0.76 ± 0.11 vs 0.93 ± 0.10 kg/cm^2, P = .32). After LVRS, there is a trend toward increased peak tension that also does not reach statistical significance (to 0.89 ± 0.08 kg/cm^2, P = .40).

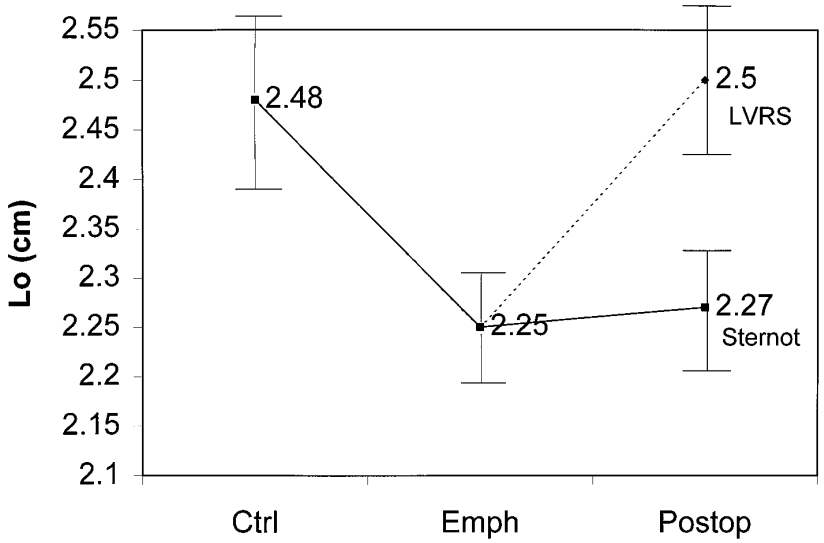

Fig 4. Time line of Lo changes after the induction of emphysema and after LVRS *(dashed line)* or sham sternotomy *(Sternot; solid line)*. Note that LVRS restores Lo to approximately its control length. Values are means ± SE.

Discussion

Of the 2 main mechanisms thought to underlie the beneficial effects of LVRS on pulmonary function, that of increased lung elastic recoil has been fairly well studied, whereas that of improved respiratory muscle function has received less attention to date. Both human[15-17] and animal[18] data suggest that there is, in fact, increased lung elastic recoil after LVRS. It is postulated that this elevated elastic recoil both increases expiratory driving force and decreases dynamic airway collapse by raising the outwardly directed forces that hold the airways open. These theories provide a reasonable physiologic explanation for the increased expiratory air flows documented after LVRS in selected patients.

In addition to increased expiratory air flows, however, most patients demonstrate marked reductions in dyspnea after LVRS. Several authors have found that there is either no correlation or, at best, a weak correlation between forced expiratory volume in 1 second and dyspnea in both unoperated patients with emphysema[19] and after LVRS.[17] These findings are consistent with a large body of information accumulated over the last 30 years that suggests that dyspnea in chronic obstructive pulmonary disease is better related to respiratory muscle function than to airflow obstruction.[20,21] It is likely, then, that improved muscle function underlies a significant component of the improvement in dyspnea derived from LVRS.

Data have been accumulated establishing that inspiratory respiratory muscle function is improved in human subjects after LVRS.[3-6] The mechanism by which this improvement is proposed to occur is a partial reversal of the deleterious consequences of severe emphysema on these muscles, most notably the diaphragm. In emphysema the diaphragm is depressed and shortened, losing its zone of apposition to the lower thoracic cage and its ability to act in a piston-like fashion to increase negative intrathoracic pressure. After LVRS, postoperative radiograms show that the diaphragm rises to a more elevated physiologic position, restoring the zone of apposition and, presumably, the piston-like action.

It is not clear on closer consideration of the muscle biology involved, however, that the diaphragm will function better simply by reassuming its former, more elevated, position. In emphysema microanatomic changes occur within the diaphragmatic muscle that are adaptative in its shortened depressed state but might be counterproductive after LVRS. Specifically, as the diaphragm shortens, it loses sarcomeres in series, reducing Lo and allowing the muscle to remain close to the optimal point on its length-tension curve.[8,22] When this muscle is acutely stretched after LVRS, its actin and myosin filaments are almost certainly moved beyond their points of maximal overlap; the muscle's fibers are stretched beyond Lo. Only if Lo can readapt to the post-LVRS increase in diaphragmatic length by also increasing would one expect the muscle to perform better after LVRS.

Lahrmann and colleagues[9] recently studied dyspnea, respiratory muscle function, and other related physiologic parameters at 3 time points after LVRS in human

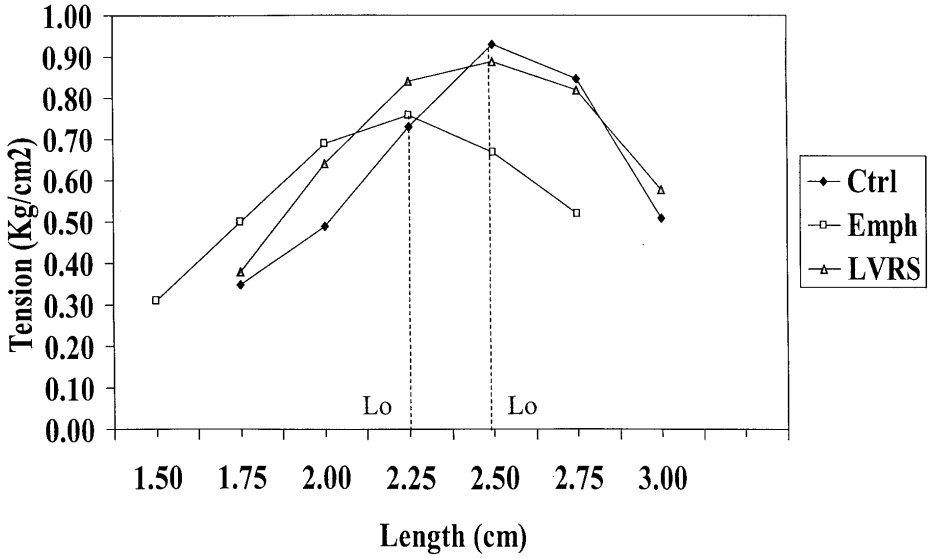

Fig 5. Diaphragmatic length-tension curves of control rats, rats with emphysema, and rats with emphysema after LVRS. Changes in Lo between groups are statistically significant (see text). Changes in peak tension between groups do not reach statistical significance (see text). Values are means, and error bars are omitted for clarity.

subjects. Their finding that improvements in respiratory muscle strength and dyspnea during loaded breathing did not reach statistical significance until the 6-month time point is entirely consistent with our theory that the diaphragm requires time to readapt to the post-LVRS state before manifesting improved function. Their further finding that, even as forced expiratory volume in 1 second and lung volumes began to return to preoperative values 12 months after LVRS respiratory muscle function continued to improve, suggests that muscle function may be more important a basis than expiratory airflow of the symptomatic relief that these patients experience. Of all the studies documenting increased respiratory muscle strength after LVRS, only one[3] demonstrated these improvements less than 3 months after the operation.

In our study we chose to evaluate length adaptation in diaphragm 5 months after LVRS. This time point was chosen because, before knowledge of the data of Lahrmann and colleagues,[9] we believe that this would be a period of time likely to be sufficient for muscle length adaptations to occur. Our results suggest that this is the case. By 5 months after LVRS, both Lo and in situ length have returned to close to the preoperative values. As shown in Fig 5, the adaptation in Lo returned the muscle to the optimal point on its length-tension curve. We suspect, although we do not present data proving this in the current study, that if one measured the same parameters 1 month after LVRS, one would find in situ length to be increased but Lo to lag behind (ie, one would find that the muscle is initially stretched beyond Lo). This would place the muscle on a suboptimal point on its length-tension curve, reducing inspiratory force until additional Lo adaptation occurred.

Also visible in Fig 5 is a difference in the maximal twitch force generated by the diaphragm strips at Lo. Although these changes have *P* values of only .32 and .40 (see "Results" section), the fact that twitch force is increased after LVRS to nearly its control value is intriguing. If this finding is confirmed with additional animals, it would suggest intrinsic changes within the muscle, resulting in increased contractility that cannot be accounted for by length changes alone. This is an area for potential future study.

Our technique of LVRS in this study resected only approximately 10% of the rats' lung volume. Thus, although statistically significant, length changes identified after LVRS did not reach the magnitude of what might be expected after LVRS as it is currently performed in human subjects. In a subsequent cohort we have performed LVRS with a low mortality rate in emphysematous rats, with resection of the entire right upper and middle lobes, as well as a larger portion of the left lung, increasing the percentage of lung volume resected to approximately 30%. It will be interesting to see what effect increased resection volume has on our findings.

An additional shortcoming of this study is the fact that true plethysmographic volumes were not determined. We relied on MELV, which is in fact a measure

of compliance, to document that emphysema had been induced in the animals. There is sufficient literature on elastase-induced emphysema in rodents to render further documentation of increased lung volumes in this model redundant. Finally, we did not study expiratory air flows in these animals, and we make no claims regarding the suitability of this model to evaluate the effects of LVRS on this parameter.

One complicating finding of this study is that in emphysematous rats (and normal rats as well), the diaphragm appears to operate at slightly below its optimal length; that is, Lo determined on the strip is greater than in situ length. This means that the rat diaphragm normally operates on the ascending limb of its length-tension curve, such that small increases in in situ length (eg, after LVRS) will displace the diaphragm closer to Lo, thus increasing its force-generating capacity. It is only larger increases in diaphragm length (changes greater than the difference between in situ length and Lo) that would require Lo adaptation to preserve diaphragmatic function. This concept may have significance in determining the optimal amount of lung to resect in patients with emphysema undergoing LVRS.

In sum, we have shown that 5 months after LVRS in emphysematous rats, not only in situ length, but also Lo, have returned to close to the nonemphysema values. We suggest that this Lo adaptation is an important physiologic basis for improvement in diaphragmatic function after LVRS. Whereas changes in elastic recoil are likely to be immediate, improvement in muscle function after LVRS likely requires several months and may be more responsible for the ongoing symptomatic relief that patients experience beyond the early postoperative period. By inference from earlier findings in rodents after the induction of emphysema, one might hypothesize that Lo adaptation after LVRS occurs by addition of sarcomeres in series. This question bears further investigation.

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