

IMPROVEMENT IN PULMONARY FUNCTION AND ELASTIC RECOIL AFTER LUNG-REDUCTION SURGERY FOR DIFFUSE EMPHYSEMA

FRANK C. SCIURBA, M.D., ROBERT M. ROGERS, M.D., ROBERT J. KEENAN, M.D., WILLIAM A. SLIVKA, JOHN GORCSAN III, M.D., PETER F. FERSON, M.D., JOHN M. HOLBERT, M.D., MANUEL L. BROWN, M.D., AND RODNEY J. LANDRENEAU, M.D.

Abstract Background. Pulmonary function may improve after surgical resection of the most severely affected lung tissue (lung-reduction surgery) in patients with diffuse emphysema. The basic mechanisms responsible for the improvement, however, are not known.

Methods. We studied 20 patients with diffuse emphysema before and at least three months after either a unilateral or a bilateral lung-reduction procedure. Clinical benefit was assessed by measurement of the six-minute walking distance and the transitional-dyspnea index, which is a subjective rating of the change from base line in functional impairment and the threshold for effort- and task-dependent dyspnea. Pressure-volume relations in the lungs were measured with static expiratory esophageal-balloon techniques, and right ventricular systolic function was assessed by echocardiography.

Results. The patients had significant improvement in the transitional-dyspnea index after surgery ($P < 0.001$). The mean (\pm SD) coefficient of retraction, an indicator of elastic recoil of the lung, improved (from 1.3 ± 0.6 cm of water per liter before surgery to 1.8 ± 0.8 after, $P < 0.001$).

Sixteen patients with increased elastic recoil had a greater increase in the distance walked in six minutes than the other four patients, in whom recoil did not increase ($P = 0.02$). The improved lung recoil led to disproportionate decreases in residual volume as compared with total lung capacity (16 percent vs. 6 percent), but the decreases in both values were significant ($P < 0.001$). Forced expiratory volume in one second increased (from 0.87 ± 0.36 to 1.11 ± 0.45 liters, $P < 0.001$). End-expiratory esophageal pressure also decreased ($P = 0.002$). These improvements in lung mechanics led to a decrease in the partial pressure of arterial carbon dioxide from 42 ± 6 to 38 ± 5 mm Hg ($P = 0.006$). Furthermore, the fractional change in right ventricular area, an indicator of systolic function, increased from 0.33 ± 0.11 to 0.38 ± 0.10 ($P = 0.02$).

Conclusions. Lung-reduction surgery can increase the elastic recoil of the lung in patients with diffuse emphysema, leading to short-term improvement in dyspnea and exercise tolerance. (N Engl J Med 1996;334:1095-9.)

©1996, Massachusetts Medical Society.

LUNG-reduction surgery in patients with diffuse emphysema involves resection of the most severely affected regions of diseased lung tissue. Recent surgical advances have increased interest in this procedure and led to its greater availability.¹⁻⁴ This surgery improves lung function by increasing airway conductance and the ratio of conductance to lung volume, possibly by increasing elastic recoil of the lung,^{5,6} which is known to increase after large bullae are removed.⁷⁻¹⁰

Because elastic recoil of the lung is the effective pressure driving maximal expiratory flow, an increase after surgery should improve flow proportionately at all lung volumes and secondarily reduce hyperinflation of the lung.^{11,12} To evaluate the effect of lung-reduction surgery on elastic recoil of the lung in patients with diffuse emphysema, we measured static transpulmonary pressures, indexes of lung volume, expiratory flow, gas exchange, and right ventricular function before surgery and three to four months afterward. We evaluated the overall clinical effect of these changes by measuring the transitional-dyspnea index and the distance a patient was able to walk in six minutes.

METHODS

Selection of Patients

We studied 20 consecutive patients with diffuse confluent emphysema documented by high-resolution computed tomography of the

lungs between October 1994 and February 1995. Patients were excluded if they had giant bullae,¹³ clinically dominant bronchiectasis or chronic bronchitis, clinical cor pulmonale or an estimated systolic pulmonary-artery pressure greater than 50 mm Hg as measured by Doppler echocardiography, if they had a history of severe epistaxis, or if they refused or could not tolerate esophageal-balloon placement.

All the patients in the study had severe dyspnea despite maximal medical therapy and had been clinically stable for at least one month before the first study. All had a ratio of forced expiratory volume in one second to forced vital capacity of less than 0.5 and a residual volume greater than 140 percent of the predicted value after a bronchodilator was administered. The protocol was approved by the institutional review board of the University of Pittsburgh, and all the patients provided written informed consent.

Surgical Approach

The resections were performed with unilateral thoroscopic techniques combining the use of a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser with stapling (in 17 patients) or bilateral median sternotomy with stapling (in 3 patients), with a goal of reducing the volume of each lung operated on by 20 to 30 percent.^{2,3} High-resolution computed tomography and nuclear-perfusion studies were performed preoperatively to identify the areas of worst anatomical disease and the regions of poorest perfusion to be targeted for resection, as well as the zones of more normal lung to be avoided. Strips of lung tissue were resected along the leading edges of each lobe — for example, along the fissures or anteriorly and posteriorly to the apex of the upper lobe and along the basal segments or superior segment of the lower lobe. An Nd:YAG laser was used adjunctively in the unilateral procedure to scarify the entire lung surface diffusely so as to inhibit the reexpansion of underlying bullae. The lung was periodically reinflated during the procedure so that the extent of resection accomplished in each lobe could be estimated to gauge the progress of the procedure and to avoid over-resection.

Clinical and Physiologic Testing

Esophageal pressure was measured as an index of pleural pressure with the use of a standard esophageal balloon-catheter system.^{14,15} With such a system, when air flow is interrupted with an occluding valve at the mouth, the difference between the esophageal pressure and the pressure in the mouth proximal to the occlusion reflects the

From the Divisions of Pulmonary, Allergy, and Critical Care Medicine (F.C.S., R.M.R., W.A.S.) and Cardiology (J.G.), Department of Medicine; the Division of Thoracic Surgery, Department of Surgery (R.J.K., P.F.F., R.J.L.); and the Department of Radiology (J.M.H., M.L.B.) — all at the University of Pittsburgh Medical Center and School of Medicine, Pittsburgh. Address reprint requests to Dr. Scirba at the Division of Pulmonary Medicine, University of Pittsburgh, 1117 Kaufman Bldg., 3471 Fifth Ave., Pittsburgh, PA 15213.

Supported by a grant from the George Love research fund.

static elastic-recoil pressure across the lung. The maneuver, first performed at maximal inflation (maximal elastic-recoil pressure), is repeated at several lower lung volumes to generate a volume–pressure curve (Fig. 1). Patients with emphysema are known to have abnormally low elastic recoil for any given lung volume, which results in a leftward shift of the volume–pressure curve. The coefficient of retraction — the ratio of the maximal static recoil pressure to total lung capacity — has been validated as a sensitive indicator of elastic recoil; decreases in this value correspond closely to qualitative leftward shifts in the volume–pressure curve.^{16,17}

The lung-recoil studies and other tests were performed one to four

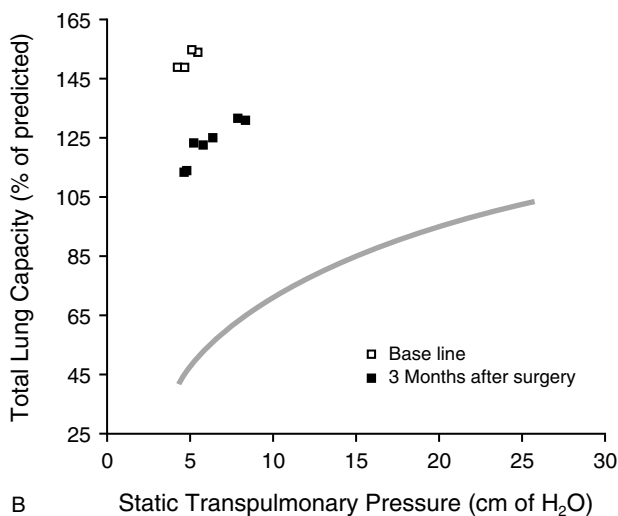
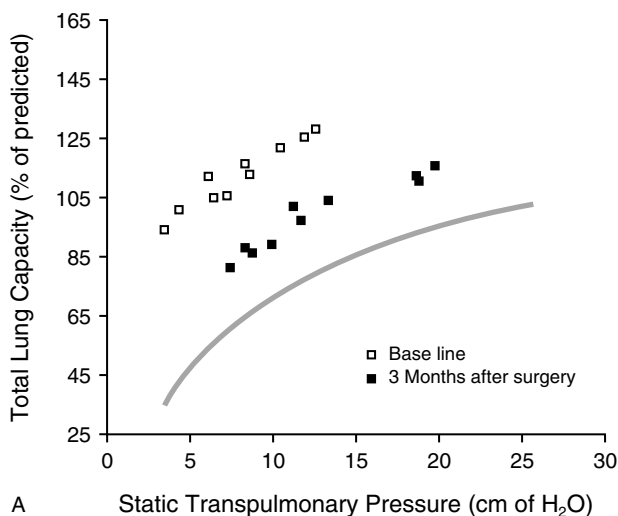


Figure 1. Relation between Lung Volume as a Percentage of Total Lung Capacity and Static Transpulmonary Pressure in Two Patients with Diffuse Emphysema.

The graphs show a shift to the right in transpulmonary pressure at a given lung volume after lung-reduction surgery (solid squares), as compared with preoperative values (open squares). The curves represent the response in normal subjects. Panel A shows the results in a 64-year-old woman with severe emphysema who had a forced expiratory volume in one second of 41 percent of the predicted value and in whom measurements could be made throughout expirations (shown are composite data points from three separate expirations). Panel B shows the results in a 41-year-old woman with more advanced disease (forced expiratory volume in one second, 12 percent of the predicted value), who could tolerate only one to two occlusions at the higher lung volumes (shown are data from two separate expirations) so that results could not be obtained at a lower lung volume.

weeks before and three to four months after lung-reduction surgery and within two hours after a bronchodilator was administered. The equipment used included a 10-cm esophageal balloon catheter (Erich Jaeger, Würzburg, Germany), a differential pressure transducer (model MP45-871, Validyne Engineering, Northridge, Calif.), a pneumotachograph (model 3700, Hans Rudolph, Kansas City, Mo.), and a pneumatic occlusion valve (model 9340, Hans Rudolph). Data were displayed with the use of commercial software (Respiratory Pressure Module, Medical Graphics, St. Paul, Minn.) but were processed independently of this system. Pressure transducers were calibrated and balloon integrity assessed immediately before, after, and when necessary, during each procedure. After three full inspirations to establish a consistent volume history, static transpulmonary pressure was measured during exhalation when pressure plateaued during two-second occlusions. When possible, measurements made during at least three reproducible exhalations were averaged. In patients with severe dyspnea, however, values were considered acceptable if maximal recoil pressure was reproduced within 1 cm of water in at least two separate maneuvers. The technologist performing the postoperative tests did not know the preoperative values, but otherwise the balloon-insertion distance and volume (0.5 ml) were identical during both tests. Although we did not establish equivalent esophageal compliance before and after the procedure, theoretical changes related to postoperative pleural fibrosis would be expected to cause us to underestimate any postoperative increase in elastic recoil.

Patients performed a six-minute walk on an oval track after receiving standard instruction.¹⁸ Supplemental oxygen was titrated before testing to determine a flow rate that would maintain arterial saturation above 90 percent during exertion at a normal pace. The transitional-dyspnea index was assessed at three months by a trained nurse clinician through direct interviews with patients. This index measured the change from base line in three categories: functional impairment, the magnitude of the task needed to evoke dyspnea, and the magnitude of the effort needed to evoke dyspnea. Scoring ranged from -9 (major deterioration) to $+9$ (major improvement).¹⁹

Measurements of esophageal pressure at functional residual capacity were recorded at end-tidal points of no flow during steady-state breathing at rest. The esophageal-pressure transducer was balanced against atmospheric pressure. Spirometry and tests of lung volume and single-breath diffusing capacity were performed with the use of standard techniques (rolling-seal spirometer, modified model 2200, Sensor-Medics, Yorba Linda, Calif.; pressure body plethysmograph, model 1085, Medical Graphics, St. Paul, Minn.) and reference equations.²⁰⁻²³ Curves for reference volume (represented as the percentage of predicted total lung capacity) in relation to pressure were those of Knudson et al.²⁴ Arterial blood for gas measurements was obtained by radial arterial puncture (ABL model 620, Radiometer, Copenhagen, Denmark).

Two-dimensional echocardiography (model 77035A, Hewlett-Packard, Andover, Mass.) was used to measure the right ventricular area. The change in area during cardiac contraction was calculated as (end-diastolic area minus end-systolic area) divided by end-diastolic area — an index of right ventricular systolic function.²⁵

Paired two-tailed t-tests were used to compare values before and after surgery. Simple linear regression analysis was used to assess relations between the maximal elastic-recoil pressure or coefficient of retraction and changes in lung volumes, spirometric indexes, and right ventricular function.²⁶

RESULTS

The study group comprised 12 men and 8 women with a mean age of 60 years (range, 40 to 75). The cause of the emphysema was tobacco-related in 19 patients, and 1 patient had α_1 -antitrypsin deficiency. The results of the pre- and postoperative tests of pulmonary function are shown in Table 1. After surgery, there were significant increases in the indexes of elastic recoil. The mean (\pm SD) maximal elastic recoil increased from 9.5 ± 3.2 to 12.1 ± 3.2 cm of water, and the coefficient of retraction increased from 1.3 ± 0.6 to 1.8 ± 0.8 cm of water per liter ($P < 0.001$ for both) (Fig. 2). Sixteen of the 20 patients had a shift to the right (toward normal) in the curve for volume versus transpulmonary

Table 1. Effect of Lung-Reduction Surgery on Physiologic and Clinical Indexes of Pulmonary Function in 20 Patients with Diffuse Emphysema.*

INDEX	BASE LINE	AFTER SURGERY	P VALUE
6-Minute walk (ft)†	819±284	916±286	0.05
Transitional-dyspnea index‡	—	5.1±1.8	<0.001
Maximal elastic-recoil pressure (cm of water)§	9.5±3.2	12.1±3.2	<0.001
Total lung capacity (liters)§	7.84±1.68 (139±12)	7.36±1.78 (131±17)	<0.001
Residual volume (liters)	4.85±1.06 (235±56)	4.08±0.94 (197±44)	<0.001
Functional residual capacity (liters)	5.98±1.16 (186±24)	5.22±1.30 (161±25)	<0.001
Forced expiratory volume in one second (liters)	0.87±0.36 (32±11)	1.11±0.45 (41±14)	<0.001
Forced vital capacity (liters)	2.77±1.16 (71±20)	3.14±1.15 (81±19)	<0.001
Esophageal pressure at end-expiration (cm of water)	-0.5±3.7	-3.1±2.7	0.002
Arterial PCO ₂ (mm Hg)	42±6	38±5	0.006
Arterial PO ₂ (mm Hg)	66±11	68±13	0.45
Diffusing capacity (ml/min/mm Hg)	8.7±4.7 (44±21)	9.6±3.5 (47±15)	0.15

*Plus-minus values are means ±SD. Values in parentheses are percentages of predicted values. PCO₂ denotes partial pressure of carbon dioxide, and PO₂ partial pressure of oxygen.

†To convert values from feet to meters, multiply by 0.305.

‡Measured in 18 patients.

§The coefficient of retraction is calculated as the ratio of the maximal elastic-recoil pressure to the total lung capacity.

pressure (Fig. 1 and 3), corresponding to increases in the coefficient of retraction. The recoil pressure at maximal inflation was reproducible in all patients; in some patients, however, sufficient data points were not consistently obtained at lower lung volumes to permit an assessment of compliance in the tidal-volume range, because the severity of their dyspnea prohibited them from holding their breaths long enough (Fig. 1B).

Only one patient had a substantial decrease in elastic recoil after surgery (Fig. 2). Disproportionate intrinsic airway disease was diagnosed in this 72-year-old woman, on the basis of the finding of pronounced bronchial thickening on computed tomography and normal preoperative elastic recoil, although the results of spirometry, tests of diffusing capacity, and computed tomography were consistent with severe emphysema.

The mean distance the patients could walk in six minutes increased significantly, from 819 ft (250 m) before surgery to 916 ft (279 m) afterward ($P=0.05$). The 4 patients who had no improvement in elastic recoil (change in maximal recoil pressure, <0.5 cm of water) had significantly less improvement in walking distance than the other 16 patients (a mean decrease of 102 ± 159 ft [31 ± 48 m] vs. a mean increase of 146 ± 182 ft [45 ± 56 m], $P=0.02$). The transitional-dyspnea index, determined in 18 patients, improved in all of them (mean increase, 5.1; $P<0.001$). In the two patients for whom dyspnea scores were not available, retrospective reviews of their records indicated subjective improvement in dyspnea.

The increases in elastic recoil were associated with significant reductions in total lung capacity (6 percent), residual volume (16 percent), and functional residual capacity (13 percent, $P<0.001$ for all measures) (Table 1). Forced vital capacity and forced expiratory volume in one second were significantly increased after surgery ($P<0.001$ for both). Esophageal pressure at end-expiration during steady-state tidal breathing decreased significantly ($P=0.002$). Seven of the eight patients who

had preoperative values for end-expiratory esophageal pressure of at least 0 cm of water had more normal, negative values after surgery.

Values for partial pressure of arterial carbon dioxide at rest decreased significantly, from 42 ± 6 to 38 ± 5 mm Hg ($P=0.006$); values decreased in all five patients (mean decrease, 6 mm Hg) who had preoperative hypercapnia (>45 mm Hg). Values for partial pressure of arterial oxygen at rest and diffusing capacity did not change significantly (Table 1). There was no significant difference in the number of patients requiring supplemental oxygen at rest (before surgery, 6 patients; after surgery, 5) or during low-level exertion (before surgery, 12 patients; after surgery, 11), according to criteria defined in the Nocturnal Oxygen Therapy Trial (partial pressure of oxygen, <55

mm Hg, or <60 mm Hg in the presence of cor pulmonale).²⁷

The fractional change in the area of the right ventricle during cardiac contraction increased from 0.33 ± 0.11 to 0.38 ± 0.10 after surgery ($P=0.02$) (Fig. 4). There was no significant correlation between the changes in maximal elastic-recoil pressure or the coefficient of retraction and changes in lung volumes, spirometric indexes, or right ventricular function.

DISCUSSION

Abnormalities in elastic recoil of the lung play a fundamental part in the pathophysiology of the mechanical respiratory impairment that is associated with emphysema. According to models relating the loss of elastic recoil of the lung to airway obstruction, abnormally low expiratory-flow rates are consequent upon both the re-

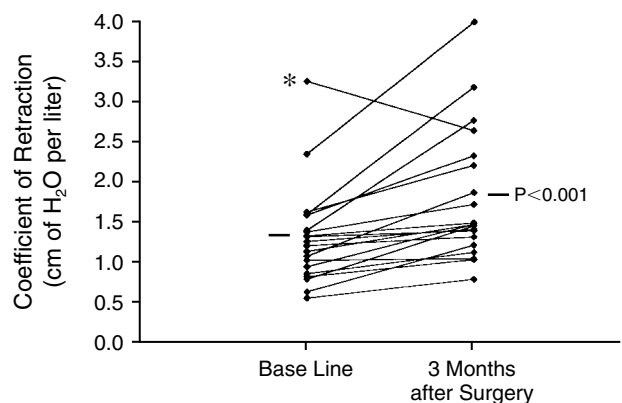


Figure 2. Coefficient of Retraction at Base Line and Three Months after Surgery in Patients with Diffuse Emphysema.

The coefficient of retraction is an indicator of elastic recoil of the lung. Values have been adjusted for differences in lung volume.¹⁶ The two horizontal bars represent the mean value at each time. The asterisk indicates the patient with a decrease in elastic recoil after surgery (see the Results section).

duction of alveolar driving pressure and increases in expiratory resistance associated with a loss in elastic airway support.^{11,12,28,29} Total lung capacity and functional residual capacity subsequently increase because of a reduction in these inward-recoil forces directed by the lung parenchyma on the chest wall. End-expiratory volume is further increased because prolonged exhalations are prematurely terminated at a volume greater than that at which the position of the chest wall and lung recoil are balanced. Airways collapse during active expiration because they are poorly tethered, and this results in further increases in residual volume. This thoracic hyperinflation leads to inspiratory-muscle inefficiency related to poorly directed muscle forces and suboptimal muscle-fiber length.³⁰ In addition, positive alveolar pressures at end-expiration, a consequence of incomplete expiration, place an added load on the inspiratory muscles that must be overcome to generate the negative intrathoracic pressures needed to initiate inspiratory flow.³¹

Our study documents clinical improvement in dyspnea and walking distance after lung-reduction surgery, and the increase in elastic recoil of the lung points to an important pathophysiologic basis for these improvements. We also confirmed the expected effect of improved lung recoil on expiratory flow rates and lung volumes. Improvements in end-expiratory flow elicited a greater reduction in residual volume than in total lung capacity, thus increasing vital capacity. It is reasonable to assume that a better respiratory-muscle configuration resulting from these changes in lung volume may have led to improved function of the respiratory muscles. The more negative end-expiratory esophageal pressures we identified after surgery strongly suggest a reduction in end-expiratory alveolar pressures, which would confer further benefits in terms of respiratory-muscle efficiency. The significant reduction in the partial pressure of

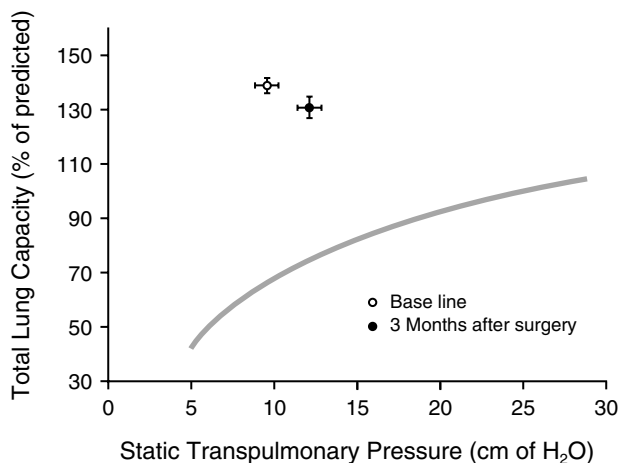


Figure 3. Mean (\pm SE) Lung Volume as a Function of Mean (\pm SE) Transpulmonary Pressure before (Open Circle) and after (Solid Circle) Lung-Reduction Surgery in 20 Patients with Diffuse Emphysema.

Note the shift to the right and downward in maximal elastic-recoil pressure and total lung capacity. Lung volume is represented as a percentage of the predicted total lung capacity. The curve represents the mean response in normal subjects.

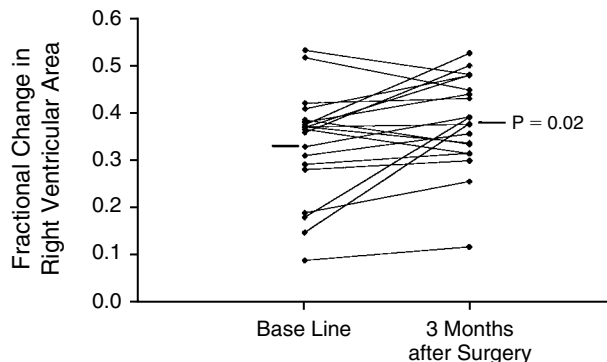


Figure 4. Fractional Change in Right Ventricular Area during Cardiac Contraction in Patients with Diffuse Emphysema before and after Lung-Reduction Surgery.

The two horizontal bars represent the mean value at each time.

arterial carbon dioxide, most likely a result of improved alveolar ventilation, is the expected outcome of these improvements in pulmonary mechanics.

The results of this study support and extend previous work that suggested that the mechanism of improvement after lung-reduction surgery was related to improved elastic recoil.⁸ In that study, short-term postsurgical increases in airway conductance and the ratio of conductance to volume were measured with body plethysmography. The results of studies of the effects of surgery on patients with giant bullae have varied; this can be explained by variation in the type of lung tissue that expanded to fill the void left by the resection of the bullae — that is, whether it was normal or diffusely emphysematous. Large bullae are often at maximal inflation and act as space-occupying regions that partially compress areas of underlying lung.³² After bullectomy, patients with normal compressed lung have increased elastic recoil and improved compliance, probably because of the effective traction applied to distant parenchyma as well as to the renewed contribution of regionally compressed normal lung to the overall pressure-volume relation.^{7,8,10} On the other hand, if the compressed lung is emphysematous, the expansion of these regions may result in only regional improvements in compliance and gas exchange and have little effect on overall mechanics.^{9,10}

In contrast to giant bullae, the areas of confluent emphysematous tissue removed by lung-reduction surgery are less commonly associated with multisegmental compression but instead exert more subtle effects on regions within lung segments. Furthermore, since these areas probably participate in air flow, even on a diminished basis, they contribute to the overall volume-pressure curve as high-compliance units. We suggest that the improved elastic recoil after this procedure is due in part to the elimination of these high-compliance regions and in part to the tethering of regional and more remote lung parenchyma. The varying magnitude of improvement in measurements of lung recoil may be related to individual variations in the pattern of disease.

The improvement in right ventricular systolic function after surgery indicates a reduction in pulmonary vascular resistance, despite the potential for the resec-

tion of partially preserved vascular tissue. This suggests that capillary recruitment may occur as a result of the improved pulmonary mechanics in lung zones previously subject to compression by hyperinflated alveoli³³ or of the tethering of extraalveolar vessels consequent on improvement in elastic recoil. Furthermore, the reduced intrathoracic pressure may augment right ventricular preload.

We have documented an improvement in elastic recoil of the lung after lung-reduction surgery in a select group of patients with diffuse emphysema; such improvement suggests a physiologic basis for the short-term clinical improvement in dyspnea, walking distance, and pulmonary function. Long-term studies will be necessary to determine the duration of these promising improvements, since there has been deterioration over time, possibly related to postoperative stress relaxation leading to the expansion of underlying smaller bullae, despite initial improvement when earlier techniques for bullectomy or unilateral lung-reduction surgery have been used.^{6,34,35}

We are indebted to Claudia Bowers, M.S.N., and Lynda Fetterman, R.N., for assistance in coordinating the project; to Dr. Michael Donahoe for review and helpful suggestions; and to Mr. Gerald Ayres and all the technologists and staff members of the pulmonary laboratory for their extra efforts.

REFERENCES

1. Wakabayashi A, Brenner M, Kayaleh RA, et al. Thoracoscopic carbon dioxide laser treatment of bullous emphysema. *Lancet* 1991;337:881-3.
2. Cooper JD, Trulock EP, Triantafyllou AN, et al. Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. *J Thorac Cardiovasc Surg* 1995;109:106-19.
3. Keenan RJ, Landreneau RJ, Sciurba FC, et al. Unilateral thoracoscopic surgical approach for diffuse emphysema. *J Thorac Cardiovasc Surg* 1996;111:308-16.
4. Benditt JO, Albert RK. Lung reduction surgery: great expectations and a cautionary note. *Chest* 1995;107:297-8.
5. Brantigan OC, Mueller E, Kress MB. A surgical approach to pulmonary emphysema. *Am Rev Respir Dis* 1959;80:194-202.
6. Rogers RM, DuBois AB, Blakemore WS. Effect of removal of bullae on airway conductance and conductance volume ratios. *J Clin Invest* 1968;47:2569-79.
7. Pierce JA, Growdon JH. Physical properties of the lungs in giant cysts: report of a case treated surgically. *N Engl J Med* 1962;267:169-73.
8. Gelb AF, Gold WM, Nadel JA. Mechanisms limiting airflow in bullous lung disease. *Am Rev Respir Dis* 1973;107:571-8.
9. Pride NB, Barter CE, Hugh-Jones P. The ventilation of bullae and the effect of their removal on thoracic gas volumes and tests of over-all pulmonary function. *Am Rev Respir Dis* 1973;107:83-98.
10. Boushy SF, Billig DM, Kohan R. Changes in pulmonary function after bullectomy. *Am J Med* 1969;47:916-23.
11. Mead J, Turner JM, Macklem PT, Little JB. Significance of the relationship between lung recoil and maximum expiratory flow. *J Appl Physiol* 1967;22:95-108.
12. Fry DL, Hyatt RE. Pulmonary mechanics: a unified analysis of the relationship between pressure, volume and gasflow in the lungs of normal and diseased human subjects. *Am J Med* 1960;29:672-89.
13. Gaensler EA, Jederlinic PJ, FitzGerald MX. Patient work-up for bullectomy. *J Thorac Imaging* 1986;1:75-93.
14. Stead WW, Fry DL, Ebert RV. The elastic properties of the lung in normal men and in patients with chronic pulmonary emphysema. *J Lab Clin Med* 1952;40:674-81.
15. Milic-Emili J, Mead J, Turner JM, Glauser EM. Improved technique for estimating pleural pressure from esophageal balloons. *J Appl Physiol* 1964;19:207-11.
16. Schleuter DP, Immekus J, Stead WW. Relationship between maximal inspiratory pressure and total lung capacity (coefficient of retraction) in normal subjects and in patients with emphysema, asthma, and diffuse pulmonary infiltration. *Am Rev Respir Dis* 1967;96:656-65.
17. Macklem PT, Becklake MR. The relationship between the mechanical and diffusing properties of the lung in health and disease. *Am Rev Respir Dis* 1963;87:47-56.
18. Guyatt GH, Sullivan MJ, Thompson PJ, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 1985;132:919-23.
19. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea: contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984;85:751-8.
20. Standardization of spirometry — 1987 update: statement of the American Thoracic Society. *Am Rev Respir Dis* 1987;136:1285-98.
21. Morris JF. Spirometry in the evaluation of pulmonary function. *West J Med* 1976;125:110-8.
22. Goldman HI, Becklake MR. Respiratory function tests: normal values at median altitudes and the prediction of normal results. *Am Rev Tuberc* 1959;79:457-67.
23. Burrows B, Kasik JE, Niden AH, Barclay WR. Clinical usefulness of the single-breath pulmonary diffusing capacity test. *Am Rev Respir Dis* 1961;84:789-806.
24. Knudson RJ, Clark DF, Kennedy TC, Knudson DE. Effect of aging alone on mechanical properties of the normal adult human lung. *J Appl Physiol* 1977;43:1054-62.
25. Oe M, Gorcsan J III, Mandarino WA, Kawai A, Griffith BP, Kormos RL. Automated echocardiographic measures of right ventricular area as an index of volume and end-systolic pressure-area relations to assess right ventricular function. *Circulation* 1995;92:1026-33.
26. Colton T. *Statistics in medicine*. Boston: Little, Brown, 1974:131-6, 191-204.
27. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med* 1980;93:391-8.
28. Christie RV. The elastic properties of the emphysematous lung and their significance. *J Clin Invest* 1934;13:295-321.
29. Pride NB, Permutt S, Riley RL, Bromberger-Barnea B. Determinants of maximal expiratory flow from the lungs. *J Appl Physiol* 1967;23:646-62.
30. Derenne JPH, Macklem PT, Roussos CH. The respiratory muscles: mechanics, control, and pathophysiology. *Am Rev Respir Dis* 1978;118:581-601.
31. Haluszka J, Chartrand DA, Grassino AE, Milic-Emili J. Intrinsic PEEP and arterial PCO₂ in stable patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1990;141:1194-7.
32. Ting EY, Klopstock R, Lyons HA. Mechanical properties of pulmonary cysts and bullae. *Am Rev Respir Dis* 1963;87:538-44.
33. Harris P, Segel N, Green I, Housley E. The influence of the airways resistance and alveolar pressure on the pulmonary vascular resistance in chronic bronchitis. *Cardiovasc Res* 1968;2:84-92.
34. Rogers RM. Stress-relaxation in pulmonary emphysema and its relation to airway conductance. *Am Rev Respir Dis* 1970;101:452-3.
35. Knudson RJ, Gaensler EA. Surgery for emphysema. *Ann Thorac Surg* 1965;1:332-62.