Innovative Approaches to Lung Volume Reduction for Emphysema*

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The 10 years of resurgent interest in lung volume reduction surgery (LVRS) and recent National Emphysema Treatment Trial findings for emphysema have stimulated a range of innovative alternative ideas aimed at improving outcomes and reducing complications associated with current LVRS techniques. Concepts being actively investigated at this time include surgical resection with compression/banding devices, endobronchial blockers, sealants, obstructing devices and valves, and bronchial bypass methods. These novel approaches are reaching the stage of clinical trials at this time. Theory, design issues, methods, potential advantages and limitations, and available results are presented. Extensive research in the near future will help to determine the potential clinical applicability of these new approaches to the treatment of emphysema symptoms. ***(CHEST 2004; 126:238–248)***

Key words: emphysema; endobronchial fenestration; lung volume reduction surgery; plugs; reducers

Abbreviations: LVR = lung volume reduction; LVRS = lung volume reduction surgery

It has now been almost 50 years since the concept of lung volume reduction surgery (LVRS) was first proposed,[1] and 10 years since interest in this concept was revived.[2,3] Many aspects of LVRS for the treatment of emphysema symptoms remain controversial.[4–9] However, extensive literature has demonstrated that carefully selected patients receive benefit in terms of symptomatic improvement and physiologic response.[10–18] The effects of LVRS on survival are uncertain at this time, despite numerous attempts to address this issue.[19–22] The National Emphysema Treatment Trial has just reported the initial study findings demonstrating survival and functional benefits in subgroups of patients undergoing volume reduction surgery,[23] and subsequent analyses should help to provide further clarification of LVRS survival issues as results become available.[8,9,17,22,24–26] A range of approaches and techniques has been used for LVRS.[2,3,25,27–38] Currently, LVRS is most commonly performed bilaterally, via thoracoscopy or median sternotomy using linear staple reduction techniques, with or without buttressing materials.[25,34,36,39–42] Much of the controversy surrounding LVRS involves the variability of response among patients, limitations in the magnitude of response, costs, and concerns about the duration of improvement.[4,5,7,22,24,43–48] Air leak remains the major morbidity following LVRS.[12,27,49]

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Given the evidence that lung volume reduction (LVR) can be beneficial, but recognizing the cost and morbidity of major surgery,[23] investigators have been vigorously pursuing research into innovative alternative methods for achieving LVR in recent years. Many of these new concepts are reaching the stage of clinical trials at this time.

There are currently the following three new general conceptual approaches to LVR for which preliminary results have been published[50–53,54]: (1) surgical resection with compression/banding devices; (2) endobronchial volume-reducing methods; and (3) endobronchial bronchial bypass approaches.

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There are theoretical approaches that need to be studied, limitations, and technical hurdles that must be overcome for each approach. Experimental data and preliminary results are becoming available for some of these approaches, and some preliminary conclusions may be drawn. It is important to review the current state of research in these areas in this rapidly advancing field.

Surgical Resection With Compression-Banding Devices

The theory behind the compression-banding approach is that external radial compressive materials or devices applied to the pleural surface of the lung could be used to reduce lung volume and allow lung resection with a lower rate of complications, particularly air leak.

One company (Spiration, Inc; Redmond, WA) has been developing a method (VALR System; Spiration Inc) that uses a biocompatible elastomeric silicone sleeve that is mechanically expanded and placed onto the lung surface to produce radial compression of the targeted lung tissue. With this approach, an elastomer sleeve is placed into a rigid tube and stretched around the distal end of the loading tube. The lung to be reduced is then drawn into the device using controlled vacuum suction (Figs 1, 2). The elastomer sleeve then is slipped off the distal end of the tube to compress the lung that was drawn up. The rigid deployment device is removed. The elastomer sleeve is now compressing the lung but can be removed up to this point if alternative placement is desired. If the position of the elastomer device is thought to be proper, the elastomer sleeve is fixed into place with a suture. The distal section of the compressed lung along with the portion of the elastomer sleeve distal to the suture site is then resected, leaving a small band of compressive elastomer fixed in place by the retaining suture.

In published investigations of this approach, effective LVR was reported in small[52] and large animal emphysema model models,[55–57] and was indicated by compliance curve responses, with minimal morbidity, and significant reduction in the incidence of air leak[52,55–57] (Figs 1–3).

The theoretical advantages of this approach include the potential reduction or elimination of air leak and reversibility after the initial application of the elastomer device (until the devices are fixed in place). Such a methodology could be relatively straightforward to apply, and rapid, incremental administration might be possible.[52,55–57]

Loading, insertion, deployment, and device fixation methods must be optimized for this approach. The design approaches may require a different methodology for application by thoracoscopy compared to median sternotomy. Biocompatibility and tissue reaction potential must be evaluated, since a band of elastomer will remain in place after the resection of the distal portion. In addition, tissue strain forces must be addressed, particularly at the sites of proximal contact between the volume reducer material edges and the lung. These issues were the focus of the preclinical animal studies,[52,55–57] and further evaluation is continuing in the clinical trial phase.

Theoretical concerns have arisen regarding the potential for chronic tissue reactions, infarction, or infection in the areas of compressed lung tissue. Several animal studies[56,57] have examined the effect of chronic compression of lung tissue in the thorax using this system. How closely the strain force and air leak responses in the animal model parallel severe emphysema in humans remains a question. Stability of the site, long-term effects, and delayed air leak questions will need to be studied carefully in clinical patient trials. In theory, air-leak may be reduced, since the lung within the elastomer segment is compressed, and stapling into emphysematous lung tissue is not necessary. However, the possibility exists that the compression may not be adequate to prevent air leaks, or that as the lung tissue necroses within the elastomer device, air leaks could develop. Such late air leak events have not been seen in the animal studies completed thus far. Efficacy and costs also must be considered. Seven patients have been treated thus far in clinical pilot studies. Efficacy data are pending.

Phase 1 acute feasibility/safety trials have been completed in a small number of patients undergoing lobectomy. Devices were implanted immediately prior to lobe resection and showed no evidence of acute air leaks during perioperative lung inflation. Lobes containing the devices then were removed. Phase 2 pilot study clinical trials in patients with severe heterogeneous emphysema are now underway using this approach.

The major apparent limitations of this approach in its current iteration are that suture fixation and manual cutting are still required, the thoracoscopic approach may be more complicated to develop due to size constraints, and questions remain regarding the effects of foreign body presence and retained necrotic tissue within the chest, with unknown consequences in emphysematous patients at this time.

Endobronchial LVR Approaches

In theory, LVR could be accomplished by the blockage or closure of conducting airways and by the

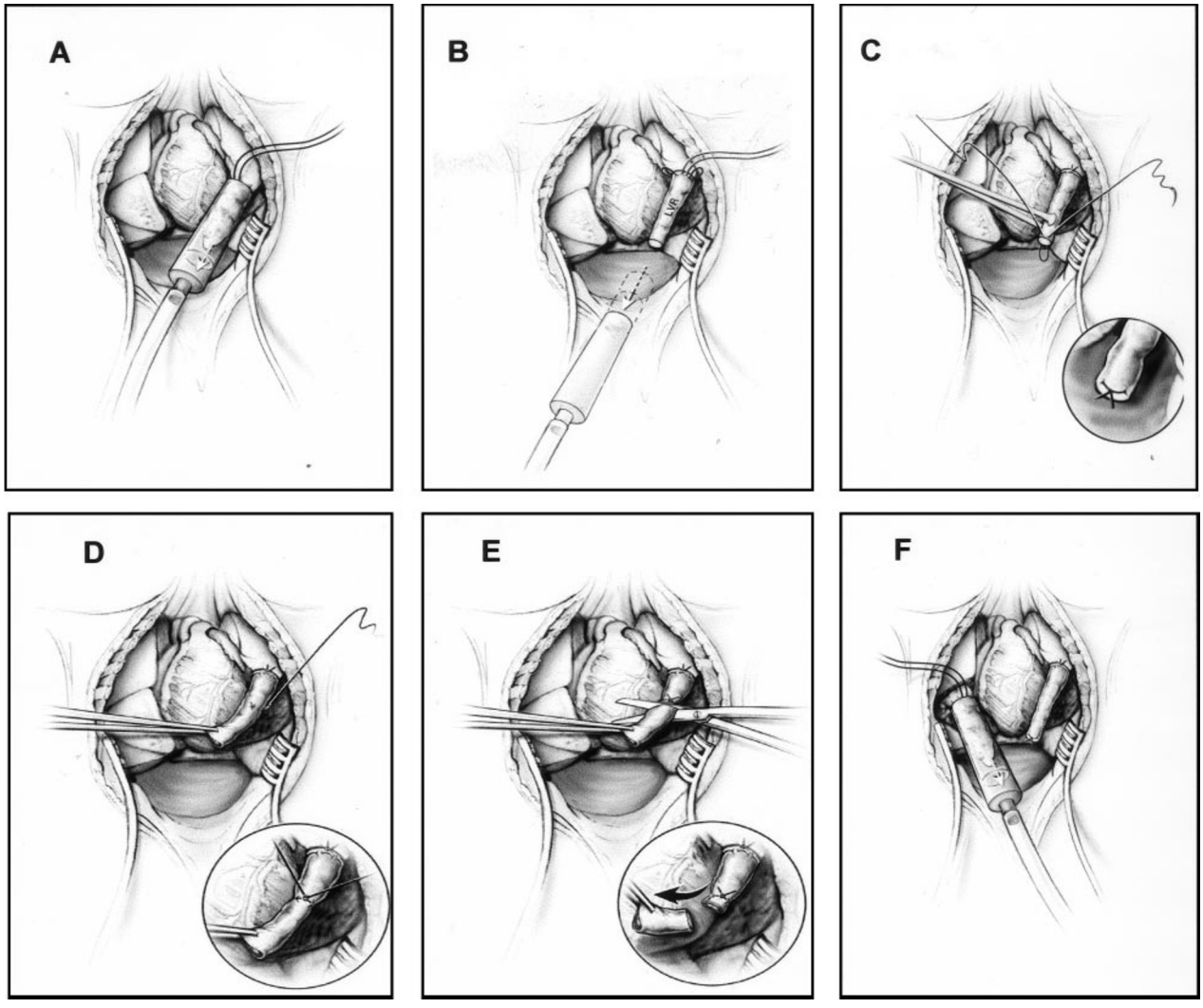

FIGURE 1. Lung volume reducer method in an animal model is shown. *Top left*, *A*: median sternotomy is performed, both thoracic cavities are entered, and the lobes are isolated. *Top middle*, *B*: the device in the vacuum column is applied to the selected lobe segment. The lung is pulled through the elastic devices by the application of negative pressure suction. The hilar end of the device is detached from the deployment column, and the column is removed, leaving the device in place. *Top right*, *C*: the hilar purse string then is tied with no more constriction than that of the existing device diameter. An apical "U" stitch is placed for further security. *Bottom left*, *D*: using the lung volume reducer as an adjunct to resection, first a U stitch is applied distal to the hilum of the lung after the proximal purse string suture is secured. *Bottom middle*, *E*: using the lung volume reducer as an adjunct to resection, the distal reduced lung is resected just distal to the applied U stitch. *Bottom right*, *F*: another view of the same procedure repeated for other selected lung regions. Reprinted with permission from *CHEST*.[52]

collapse of the distal alveoli from an endoscopic approach. A variety of methods have been proposed for this, including the injection of biopolymers or tissue glues, the installation of biologically active mediators to cause contraction and fibrosis, endobronchial valves or plugs, and/or combinations of these methods.[51,53,58]

Endobronchial Airway Sealants

Ingenito et al[58] published the first manuscript describing bronchoscopic LVR involving the installation of fibrin glue leading to regional collapse and bronchoscopic volume reduction. The theoretical advantages of this approach include the following: nonsurgical minimally invasive procedures can be used; incremental application is possible with the ability to perform repeated limited procedures; air-leak risk may be reduced or eliminated; cost reduction could be considerable; and the procedure potentially could be performed on an outpatient basis. Theoretical risks and technical hurdles that must be addressed include the potential for ventilation per-

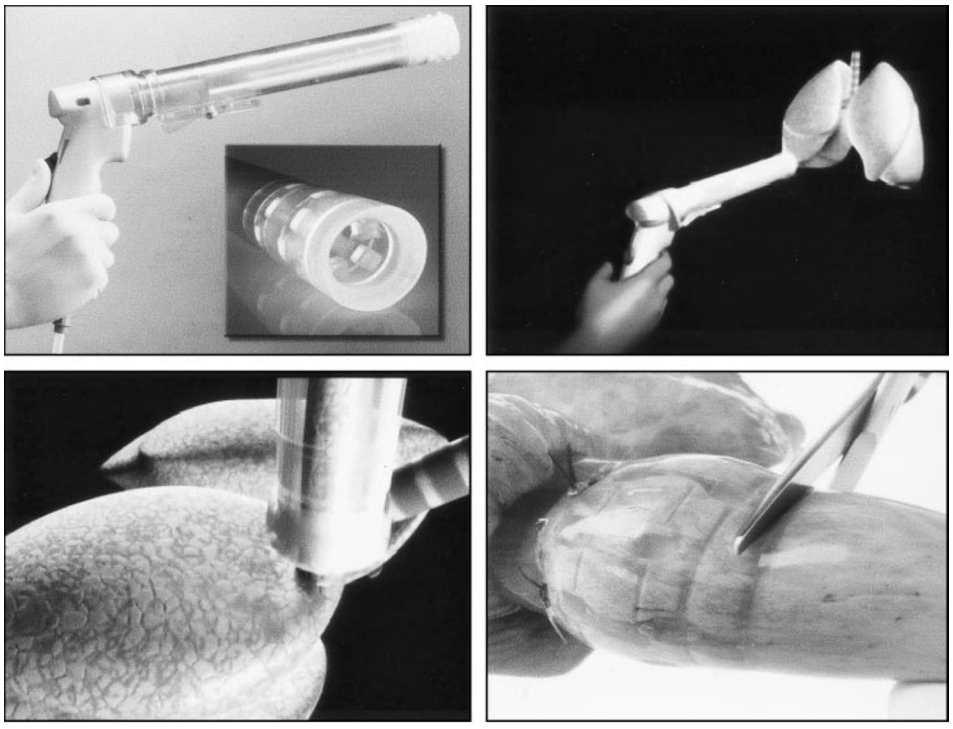

FIGURE 2. *Top left*: deployment system for external elastomer lung volume reducer in humans. *Top right*: lung volume reducer applied to the lung surface. *Bottom left*: lung drawn into the deployment device. *Bottom right*: compressed residual lung cut from suture-fixed compressive elastomer. Reprinted with permission from Spiration, Inc.

fusion mismatch and hypoxemia if lung regions with persistent pulmonary blood flow are obstructed (without concurrent elimination of the corresponding circulation). Questions arise about the risk of postobstructive infection. Methods must ensure that the occluded regions will collapse despite collateral ventilation and will not spontaneously reopen over time. In addition, it is uncertain whether the anatomic distribution effects and physiologic response of segmental or subsegmental volume reduction will provide similar results to current peripheral lung tissue reduction approaches.

Endobronchial occlusion using fibrin glue was studied in sheep with papain-induced emphysema.[59] Bronchoscopic fibrin-based LVRS installation was performed in five ventral subsegments following surfactant washout. Control groups showed the development of emphysema, without improvement following sham reduction. Standard staple LVRS and bronchoscopic fibrin-based LVR groups showed substantial and similar returns toward baseline in terms of compliance, lung volumes, and resistance[58] (Fig 4).

In animal studies,[58] this approach was limited by the incomplete effectiveness of the procedure in some regions, and by the development of sterile abscesses. Since this initial publication, considerable effort has been directed toward novel ways for overcoming these complications in preparation for clinical trials. In a subsequent approach, these researchers investigated bronchoscopic LVR using "tissue engineering principles" involving target segments treated with a "primer reagent" (0.25% trypsin in phosphate-buffered saline; Bistech Inc; Woburn, MA), followed by a "washout solution" (Washout Solution Roswell Park Memorial Institute-1640 culture media, containing 10 heat inactivated fetal bovine serum; Bistech Inc).[60] This treatment was followed by the injection of fibrin hydrogel suspension and thrombin cross-linker applied in small-volume injections. In sheep with papain-induced emphysema, they reported improvements in compliance curves and recoil pressure as well as residual volume/total lung capacity ratios following bronchoscopic LVR with this approach. No significant systemic reactions, pleural effusions, or lung abscesses were seen.[60]

Endobronchial Blockers (Plugs)

Mechanical endobronchial blockers have been designed to obstruct target airways, leading to distal collapse and bronchoscopic volume reduction. In

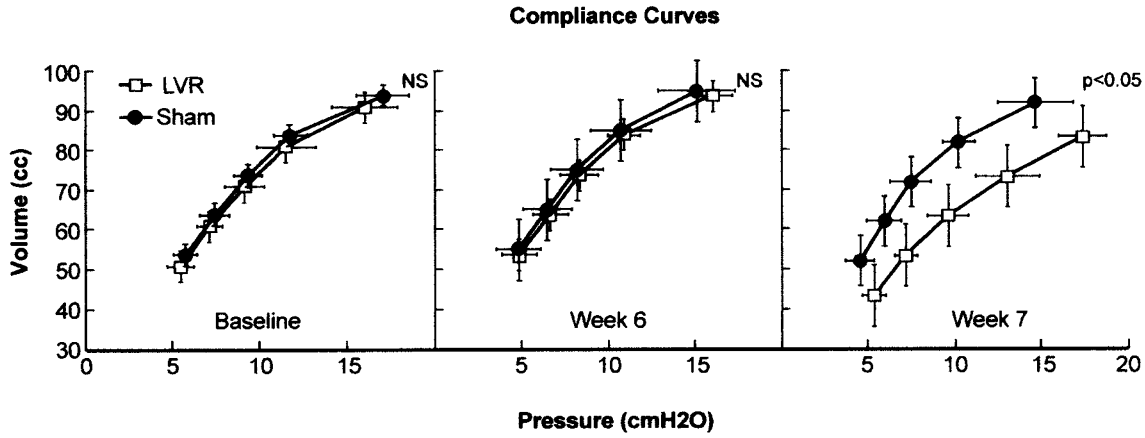

FIGURE 3. Static respiratory system compliance in emphysematous New Zealand white rabbits treated with external compressive LVR vs sham controls. Graph shows lung compliance at baseline (*left*) before induction of emphysema, preoperatively (week 6) [*middle*] after the induction of emphysema, and postoperatively (week 7) [*right*] 1 week after surgery. Repinted with permission from *CHEST*.[52]

addition to the theoretical advantages described for the fibrin-based regional volume reduction approach, an additional potential theoretical advantage of an endobronchial blocker technique includes the possibility of removing devices either immediately after deployment or after a delayed period of time. The testing of bronchial occlusion with "spigots" in patients with emphysema and persistent pneumothorax has been reported by Toma et al.[61] In this study, 23 patients received bronchoscopic implantation of spigots for persistent pneumothorax. Two patients had the whole upper lobe segments occluded and developed upper lobe collapse. The procedure caused no mortality. Additional potential limitations and technical hurdles to be overcome include the presence of an endobronchial foreign body (with risk of foreign body reactions) and the risk of postobstructive pneumonia. There is concern regarding the potential for device displacement, migration, or even erosion into regional tissue with additional theoretical concerns for bleeding. The obstruction of mucus clearance must be addressed. Most importantly, with mechanical obstruction in emphysematous patients there is a risk that collateral airflow may supply the regions distal to the obstruction to the extent that distal collapse will be ineffective.[58]

One company (Closure Medical Inc; Raleigh, NC)[54] has reported preclinical studies regarding the development of proprietary cyanoacrylate-based liquid "plugs" that polymerize in the airways when applied bronchoscopically along with a chemical activator, viscosity modifier, and radiopaque agent. In this procedure, "the bronchoscope is introduced into the desired lobe with conscious sedation. The balloon catheter is positioned within the target bronchial segment, the delivery syringe is attached and the liquid is delivered through the catheter. Subsequently, the catheter and bronchoscope are removed, once polymerization has been achieved."[54]

Preclinical studies were performed in a goat model to provide proof of concept for an occlusive device and reportedly achieved "safe and effective" atelectasis at the segmental level. A rigid bronchoscopic procedure was performed using a 6F Berenstein occlusive balloon catheter. Antibiotic therapy was administered for 7 days after the procedure, and animals were killed at 90 days. The investigators reported that the device was still in place at 90 days. No infections were reported. They concluded that this represented a successful demonstration of the concept of occlusive airway devices.[54] The investigators did not further define their criteria for "safe and effective" outcome in this presentation.[54] Information on the number of animals, whether the animals were normal or emphysematous, and functional results were not presented.[54]

Endobronchial Valves

An endoscopically deployable endobronchial valve has been described[62] with removal facilitation sites, a "one-way valve design" for mucus clearance, and anchors to maintain position (Fig 5). This valve (IBV; Spiration, Inc) uses a compressible umbrella-like valve that is loaded into a delivery catheter that fits into the working channel of a bronchoscope. The investigators described[62] deployment in four healthy swine using valves that were 4 to 8 mm in size. They reported successful deployment, ease of administration, and no migration of valves at 4 days of follow-up. They reported "effective lung reduction" based

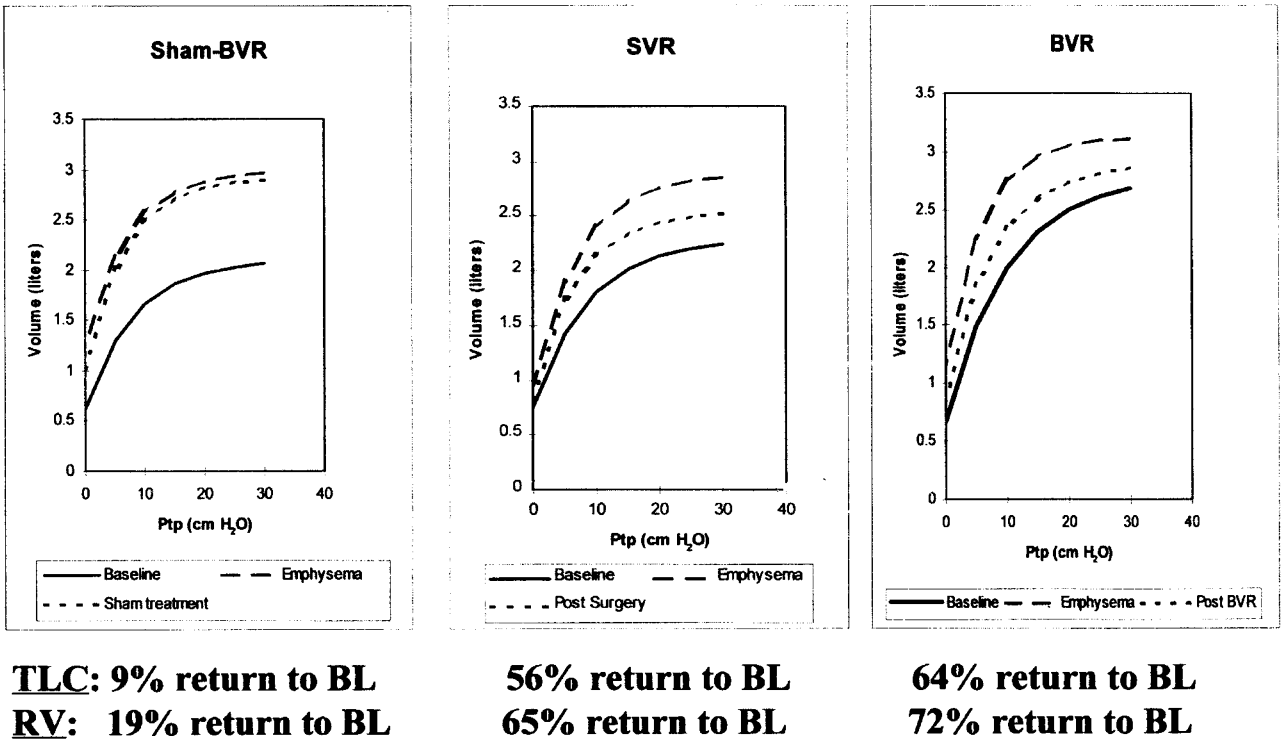

FIGURE 4. Compliance curve response to standard surgical and endobronchial volume reduction surgery in emphysematous sheep. Baseline, postpapain, and posttreatment static pressure-volume relationships are shown for animals that have undergone Sham-bronchoscopic volume reduction (BVR) [*left*], surgical volume reduction (SVR) [*middle*], and BVR (*right*). Graphs contain composite data from four animals per group. Sham treatment did not affect lung volumes. SVR and BVR produced large, significant reductions in total lung capacity (TLC) and residual volume (RV). BL = baseline; Ptp = transpulmonary pressure. Reprinted with permission from *American Journal of Respiratory and Clinical Care Medicine*.[58]

on visual inspection, but without pulmonary function analysis in the normal model. No complications were noted.[62]

In another animal study, the investigators evaluated the use of valves in single procedures or procedures combined with LVRS.[62] In this study, valves (IBV; Spiration, Inc) were placed at the time of bronchoscopy. Several days later, visual confirmation of volume reduction was obtained. Further animal model studies are reportedly ongoing at this time,[62] and the company reports that >500 valves have been placed in three different animal species with follow-up at 1, 3, and 6 months.[54] This technique also includes the possibility of removing valves either immediately after deployment or after a delayed period of time.

Another reported endobronchial blocker valve design (Emphasys Medical, Inc; Redwood City, CA) uses a nitinol retainer with "anti migration flares" to secure and stabilize the valve implant and multiple seals[51,53] (Fig 6). Mucous clearance is achieved through the one-way valve. The device has a grasping area for removal. Studies have use valves with diameters of 4 to 10 mm thus far. In the report, 10 patients aged 51 to 69 years with apical emphysema and hyperinflation, who were otherwise suitable for standard LVRS (mean preoperative FEB_1 0.72 L [19 to 46% predicted]; 6-min walk distance, 340 m [range, 245 to 425 m]) underwent treatment, with the placement of 4 to 11 valves per patient. The average length of hospitalization was 1 to 8 days, with no mortality. In this report,[51] symptomatic improvement was not in 4 of 10 patients. Minor complications included exacerbation of COPD (three patients), asymptomatic localized pneumothorax (one patient), and lower lobe pneumonia (one patient). No major change in radiologic findings, lung function, or 6-min walk distance was evident at 1 month, although gas transfer improved and nuclear upper lobe perfusion fell. Toma et al[63] reported unilateral LVR using endobronchial valves in eight patients with severe emphysema. This group found that after valve insertions, the median FEV_1 increased from 0.79 to 1.06 L (range, 0.75 to 1.22 L; difference, 34%; $p = 0.028$). CT scans have shown a substantial reduction in regional volume in four of the eight

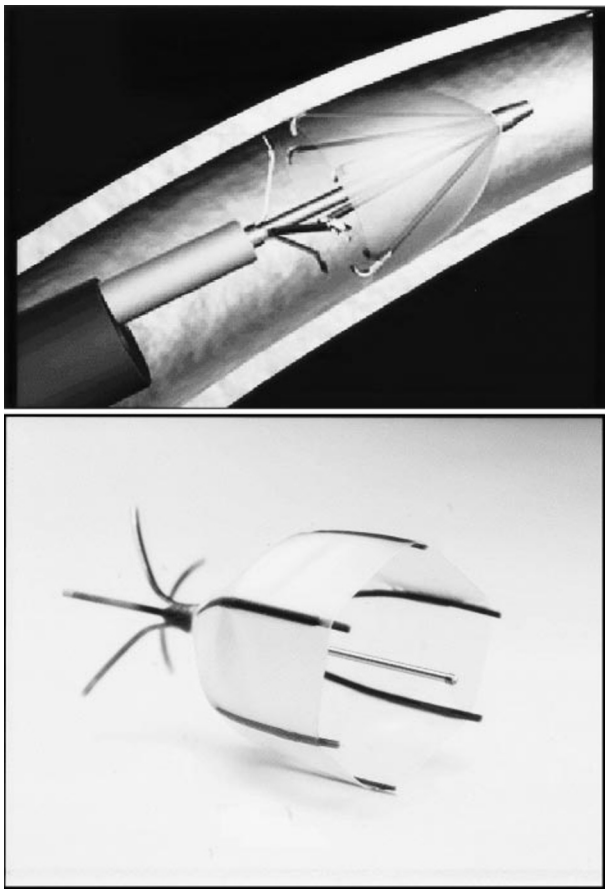

FIGURE 5. Bronchoscopic deployment of an endobronchial valve design. *Top*: endobronchial blocker with collapsible design is shown being deployed from the working channel of a standard flexible fiberoptic bronchoscope. *Bottom*: later version of the prototype device (IBV; Spiration, Inc) is shown. Reprinted with permission from Spiration, Inc.

patients, and two patients developed a transient pneumothorax (one requiring drainage). No other important adverse effects were reported during follow-up.[63]

Since the first report, 91 patients have now been treated, with > 365 valves implanted (a nine-center experience) and 14,052 patient-days of observation. The investigators have reported[54] the following: acute death, 1 patient; infections, 3 patients; pneumothorax, 8 patients; persistent cough, 1 patient; late deaths, 3 patients; and COPD exacerbations, 13 patients. In a subset of nine patients treated at the Royal Brompton Hospital, there were increases in FEV_1 comparable to those in LVRS patients, without change in FVC (four patients with substantial improvement, and three patients with no improvement).[54] There have not been published results concerning pulmonary function or exercise from the larger group of patients who have undergone valve implantation at this time. Human clinical trials are continuing.[51,53,54]

FIGURE 6. Endobronchial valve for endoscopy. One-way valve with nitinol retainer structure and flares. Reprinted with permission from Emphasys Medical, Inc.

Similar safety and effectiveness considerations regarding the endobronchial blockers apply for the administration of the endobronchial valves. The valve design and removability of these devices may have significant advantages compared to plugs to reduce the risks associated with postobstructive pneumonia. Issues regarding the valve size, the number of valves required to produce effective volume reduction, access to the different segments and subsegments of the lungs, safety, effectiveness, overcoming collateral ventilation, and ease of use may require extensive clinical investigation. Questions regarding efficacy remain and await clinical patient trials, since animal models of emphysema do not appear to demonstrate the extensive degrees of collateral ventilation that are present in patients with severe emphysema.

Bronchial Fenestration and Airway Bypass

The concept behind bronchial fenestration is that dynamic expiratory resistance in the small airways is greatly elevated in emphysematous patients, with associated increases in collateral ventilation. In order to bypass the high resistance collapsing airways segments, a direct connection between the bronchus and the collaterally ventilated lung parenchymal region is made using noncollapsible bronchial stents. This creates new conducting expiratory airways.

The procedure, recently described by Rendina et al[50] and Lausberg et al[64] involves the creation of

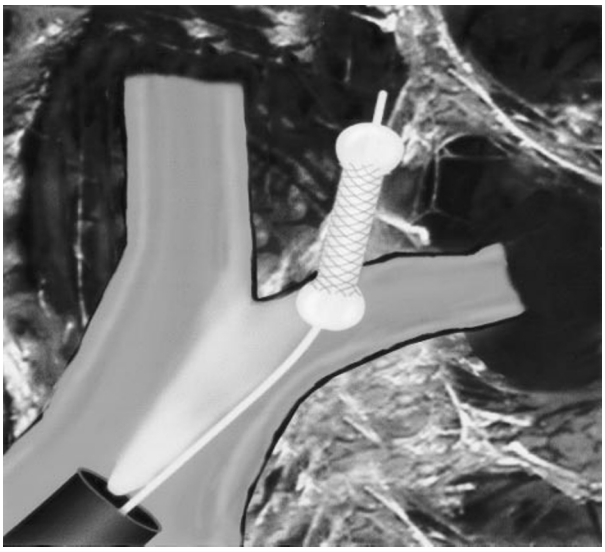

FIGURE 7. Deployment and balloon dilation of a bronchial bypass stent. Reprinted with permission from *Annals of Thoracic Surgery*.[64]

bronchial wall fenestrations using a radio frequency ablation catheter at segmental or subsegmental bronchial levels. Expandable stents (currently, 1.5 cm by 3 mm) are placed through the bronchial wall into the lung parenchyma. The bronchial stent is deployed with balloon dilatation, leaving the proximal end of the stent at the opening of the bronchial fenestration (Fig 7). Theoretical advantages of this technique include increased expiratory airflow and reduced expiratory resistance. The procedure can be performed bronchoscopically with the potential to reduce morbidity compared to open procedures.

Technical challenges and limitations include the need to reduce the risks of bleeding, since the bronchial blood vessels run adjacent to the airways. An ultrasound guidance probe (Broncus Technologies Inc; Mountain View, CA) is used to identify the locations of the adjacent vessels prior to deployment of the radioablation catheter. Questions remain regarding the ability to "entrain" large enough regions of trapped air for clinical benefit. The duration of response will need to be evaluated, since foreign body reactions and fibrosis could limit the duration and effectiveness of the bronchial fenestration method. In addition, the bronchial stents are foreign bodies directly connecting proximal airways to lung parenchyma, and risks of infection will need to be determined.

The feasibility of this concept was demonstrated using freshly excised emphysematous human lungs removed from patients undergoing lung transplantation.[50] Forced expiratory maneuvers were performed on the isolated lungs in a ventilation chamber. Marked increases in expiratory flow and volume were demonstrated following the placement of three bypass stents. Further increases were demonstrated

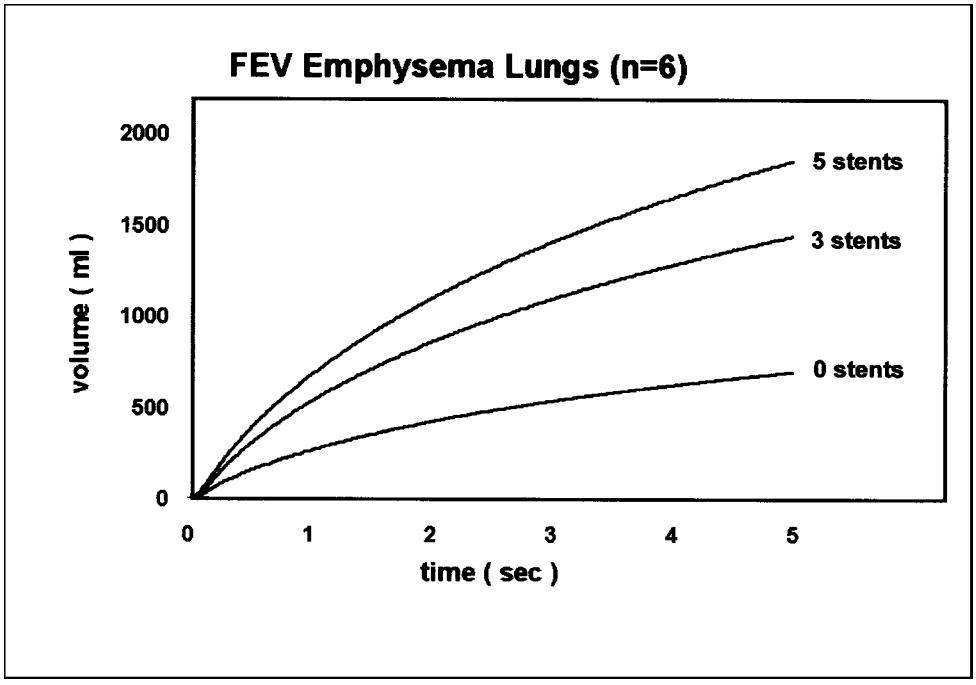

FIGURE 8. Change in expiratory flows with bronchial stents in excised emphysematous human lungs is shown. Composite data are given from six lungs. Reprinted with permission from *Annals of Thoracic Surgery*.[64]

Table 1—*Currently Reported Investigational Approaches to Volume Reduction Surgical Alternatives

Alternative LVR Concept	Specific Approach	Stage of Development Reported	Outcome Variables Reported	References
Surgical resection with compression banding	VALR biocompatible silicon sleeve compression device	Animal studies Human trials underway	Lung function, safety, morbidity, mortality, pathology	52, 55–57
Endobronchial volume-reducing methods	Fibrin glue instillation	Animal studies	Lung function, safety, morbidity, mortality, pathology	58, 59
	"Tissue engineering principles" with "primer reagents" and fibrin hydrogel solution	Animal studies	Lung function, safety, morbidity, mortality, pathology	60
Plugs	Endobronchial spigots (for air leak)	Humans	Safety, morbidity, mortality, effectiveness for sealing leaks	61
	Cyanoacrylate "liquid plugs"	Animals	Safety, visible atelectasis	54
Valves	Umbrella device (IBV)	Animals	Lung function, safety, morbidity, mortality, pathology	54, 62
	Valves with nitinol retainers	Human studies	Safety, morbidity, mortality. Limited series lung function	51, 53, 54, 63
Endobronchial bypass (fenestration)	Wire bypass stents through bronchial walls	Animal studies, short-term human safety reports	Lung function, safety, morbidity, mortality (animals); acute safety (humans)	50, 64

*Thus far, no randomized, controlled trials for these approaches have been performed. VALR = vacuum assisted lung resection system (Spiration; Redmond, WA).

after the placement of additional stents (Fig 8). In contrast, no change in expiratory flow was demonstrated in healthy excised lungs. Safety studies in patients undergoing pneumonectomy have been successfully performed. Human clinical effectiveness trials are underway.

Questions that will need to be examined in upcoming laboratory and clinical studies include investigations on the mechanisms of increased expiratory flow with fenestration bypass. Such studies will be important in the further evaluation of selection criteria and materials, as well as size, shape, design, and number of stents to be placed. Optimal stent locations and types of stents will require extensive evaluation. The duration of response will be a major focus of inquiry.

Summary

There are a number of recently described innovative approaches to LVR for the treatment of emphysema symptoms under active investigation (Table 1). The general concepts behind these approaches include external compression, endobronchial obstruction or valves, and bronchial bypass methods. Data are emerging at this time from animal studies and some preliminary human investigations. Some of the preliminary data appear to show promise, although it is too early to draw firm conclusions regarding the likelihood of success for any or all of these innovative concepts.

The external compressive LVR concept may be somewhat closer to clinical application at this time, with relatively close parallels in physiologic concept to current LVRS techniques. Endobronchial valves are the subjects of intensive active investigation at this time, and more definitive data should be available in the near future. Bronchial fenestration is being proposed for patients with more homogeneously distributed disease, who are currently considered to be poor candidates for LVRS. This technique has a number of substantial technical hurdles to be overcome before clinical effectiveness is likely to be defined.

Overall, extensive research in the near future will help to determine the potential clinical applicability of these new approaches to the treatment of emphysema symptoms.

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