



Lung Volume Reduction Therapies for Advanced Emphysema

An Update

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Observational and randomized studies provide convincing evidence that lung volume reduction surgery (LVRS) improves symptoms, lung function, exercise tolerance, and life span in well-defined subsets of patients with emphysema. Yet, in the face of an estimated 3 million patients with emphysema in the United States, < 15 LVRS operations are performed monthly under the aegis of Medicare, in part because of misleading reporting in lay and medical publications suggesting that the operation is associated with prohibitive risks and offers minimal benefits. Thus, a treatment with proven potential for palliating and prolonging life may be underutilized. In an attempt to lower risks and cost, several bronchoscopic strategies (bronchoscopic emphysema treatment [BET]) to reduce lung volume have been introduced. The following three methods have been tested in some depth: (1) unidirectional valves that allow exit but bar entry of gas to collapse targeted hyperinflated portions of the lung and reduce overall volume; (2) biologic lung volume reduction (BioLVR) that involves intrabronchial administration of a biocompatible complex to collapse, inflame, scar, and shrink the targeted emphysematous lung; and (3) airway bypass tract (ABT) or creation of stented nonanatomic pathways between hyperinflated pulmonary parenchyma and bronchial tree to decompress and reduce the volume of oversized lung. The results of pilot and randomized pivotal clinical trials suggest that the bronchoscopic strategies are associated with lower mortality and morbidity but are also less efficient than LVRS. Most bronchoscopic approaches improve quality-of-life measures without supportive physiologic or exercise tolerance benefits. Although there is promise of limited therapeutic influence, the available information is not sufficient to recommend use of bronchoscopic strategies for treating emphysema. *CHEST 2010; 138(2):407-417*

Abbreviations: 6MWD = 6-min walk distance; ABT = airway bypass treatment; BET = bronchoscopic emphysema treatment; BioLVR = biologic lung volume reduction; EBV = Endobronchial Valve; FDA = US Food and Drug Administration; HD = high dose; IBV = Intrabronchial Valve; LD = low dose; LE = lobar exclusion/collapse; LVR = lung volume reduction; LVRS = lung volume reduction surgery; LVT = lung volume therapy; MCID = minimal clinically important difference; mMRC = modified Medical Research Council; NETT = National Emphysema Treatment Trial; PLLD = predominant lower lobe disease; PULD = predominant upper lobe disease; QOL = quality of life; RCT = randomized clinical trial; RV = residual volume; SGRQ = St. George Respiratory Questionnaire; TLC = total lung capacity; VENT = Endobronchial Valve for Emphysema Palliation Trial

Pulmonary emphysema is common, chronic, progressively disabling, and eventually fatal. The disease is caused by cigarette smoking in 80% to 90% of the cases. The pathologic process destroys and hyperinflates alveoli, reduces lung elastic recoil, and impairs gas exchange. The pathophysiology is compounded by compromised ventilation as the hyperinflated lungs are entrapped in a nonpliable chest cage and cannot expand adequately during inspiration. The most

debilitating clinical manifestations of emphysema are dyspnea and reduced exercise tolerance. In the advanced phases, the patient is breathless during

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ordinary activities and eventually even at rest. At this stage palliation becomes a more relevant treatment goal than increased longevity.

Medical treatment of emphysema offers modest symptomatic relief but does not halt disease progression. Several surgical therapies were proposed during the last century but none proved useful until Brantigan, in 1956, resected the most diseased portions of the emphysematous lungs (lung volume reduction surgery, LVRS) in an attempt to diminish the size mismatch between lung and chest cage and to improve the mechanics of the remaining organ.¹ The operative mortality was 16%, but many who survived surgery experienced subjective improvement. Unfortunately, corroborative physiologic measurements were not obtained and LVRS was not accepted as effective therapy.

Using modern surgical technology combined with careful patient selection, Cooper et al² reintroduced LVRS in 1995 with reduced operative mortality (4.8%). The improvements in symptoms were corroborated with pulmonary function, exercise tolerance, and quality of life (QOL) measures. The gratifying results were reproduced by others and a wave of enthusiastic LVRS use followed.³⁻⁵ A metaanalysis of six small randomized clinical trials (RCTs), incorporating 306 patients, also showed favorable results (Table 1).⁹

In 1996, the Centers for Medicare and Medicaid Services and the National Institutes of Health cosponsored a 17-center nationwide RCT, the National Emphysema Treatment Trial (NETT). From 3,997 patients screened, 1,218 were enrolled. An interim analysis identified 140 patients as “high risk for LVRS” and enrollment from this category was halted.¹⁰ The outcomes from the remaining 1,078 individuals confirmed that in selected cohorts LVRS confers durable symptomatic, physiologic, and survival benefits with a 5.5% mortality, >50% morbidity, and substantial financial outlay (Table 1).¹¹ In an attempt to reduce the risks and cost associated with LVRS a search for nonsurgical approaches ensued. The purpose of this article is to present an updated analysis on

available information about LVRS and bronchoscopic approaches to lung volume therapy (LVT, bronchoscopic emphysema treatment [BET]), propose a system for validation of emerging procedures, and provide an evidence-based estimate on potential use.

LVRS

Cooper and colleagues² concluded from their experience that favorable outcomes from LVRS require (1) selection of appropriate patients, and (2) multidisciplinary team approach by pulmonologists, thoracic surgeons, and other relevant specialists. Adherence to these standards resulted in reproducible symptomatic and physiologic improvements.^{3-5,9}

Patient Selection for LVRS

The basics of inclusion and exclusion criteria proposed by Cooper et al² and NETT have been widely adopted. The criteria were modified, however, by NETT and others.^{5,11} (Table 2).

Results From LVRS

NETT reproduced the favorable results obtained from LVRS in earlier observational and small randomized studies, especially in patients with predominantly upper lobe disease (PULD).¹¹ The strengths of NETT lie in its randomized design; sizable enrollment; robust multidimensional physiologic, radiographic, and QOL data set cost analysis facilitated by a single payer (Medicare); and 5-year survival follow-up.

The 90-day 5.5% operative mortality experienced by NETT’s “non-high-risk patients” is consistent with the national experience but figures of 1.2% and less have also been reported.^{3,5} Serious morbidity of approximately 50%, consisting mostly of major air leaks and, to a lesser extent, of respiratory failure, pneumonia, cardiac arrhythmias, endotracheal reintubation, and tracheostomy were similar to those encountered by other randomized and observational studies.^{2,11-13}

The 1,078 non-high-risk patients fell into four outcome categories based on anatomic distribution of emphysema and level of baseline exercise tolerance with the PULD and low baseline exercise tolerance combination showing the most favorable response to LVRS.¹¹ Pulmonary function, exercise capacity, and QOL measures were statistically and clinically superior to those in medical controls and were sustained 3 and 4 years after the operation, respectively (Table 3).

The 5-year survival advantage for LVRS over the medical arm showed a risk ratio (RR) for death of 0.86 ($P = .02$).^{9,13} Using NETT data obtained under the Freedom of Information Act, Sanchez and colleagues⁷ noted that the 5-year survival for the LVRS/PULD cohort was superior to that of the medical control

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Table 1—Lung Volume Reduction Surgery Outcomes

Study	No. Patients	FEV ₁ , %			RV, %			6MWD, m			SGRQ, units			Survival, %			
		Follow-up, mo			Follow-up, mo			Follow-up, mo			Follow-up, mo			mo			
		6	12	36	6	12	36	6	12	36	6	12	36	3	12	36	60
Observational ^a																	
Ciccone et al, ⁶ PULD, PLLD	250	57 ^b	43 ^b	29 ^b	-31 ^b	-29 ^b	-28 ^b	61 ^b	61.1 ^b	39 ^b	n/a	94	90	84	67
Randomized																	
NETT PULD ⁷																	
LVRS ^a	261	44 ^b	38 ^b	34 ^c	-31 ^b	-27 ^b	-24 ^b	60 ^b	52 ^b	n/a	-17 ^b	-17	-12 ^b	95	...	81 ^c	70 ^d
Medical Rx ^a	250	0	12	12	0	0	-1.2	4	0.7	n/a	-2	0	0	98	...	74	60
Metaanalysis ^{9,c} 6 RCTs; PULD	167/139 ^f	29 ^b	39 ^b	46 ^g	96/94 ^f
Lung Tx for COPD ⁸	81	64	49

LVRS results from an observational study, the NETT, and metaanalysis of six small RCTs. 6MWD = 6-min walk distance; LVRS = lung volume reduction surgery; n/a = not applicable; NETT = National Emphysema Treatment Trial; PLLD = predominant lower lobe disease; PULD = predominant upper lobe disease; RCT = randomized clinical trial; RV = residual volume; Rx = treatment; SGRQ = St George Respiratory Questionnaire; Tx = transplant.

^aChanges from baseline.

^bP ≤ .001.

^cP ≤ .05.

^dP = .02.

^eDifference between randomized arms.

^fLVRS/medical treatment.

^gP = .0002.

subjects and almost identical to the 250-patient heterogeneous LVRS observational experience of Ciccone et al (Fig 1).⁶ NETT's upper-lobe LVRS cohort also exhibited better 5-year survival than patients having lung transplants for COPD.⁸

Communications in the literature also describe patients with severely compromised pulmonary function from emphysema in whom the risks of cardiac

surgery or resection for lung cancer were deemed prohibitive but who tolerated the indicated surgery when it was combined with LVRS.^{14,15}

Following publication of NETT's results, Centers for Medicare and Medicaid Services extended LVRS coverage for patients belonging to NETT outcome categories 1, 2, and 3, but not category 4 (Table 3).¹⁶ Despite the strong evidence of the palliative and survival benefits from LVRS, only 258 operations were performed between January 2004 and September 2005 under the aegis of Medicare.¹⁷ The surprisingly low use may be due in part to a prevailing impression generated in part by misleading reporting in effect that LVRS is minimally effective with unacceptably high morbidity and mortality.¹⁸⁻²⁰

BET

The LVRS experience established that lung volume reduction is on sound clinical and physiologic grounds.²¹ Several nonoperative bronchoscopic approaches have been developed in an attempt to reap the benefits of LVRS but at lower risks and costs. Data sufficient for analysis are available from the following strategies:

1. Deployment of unidirectional valves into the airways to collapse the targeted lung parenchyma and decreased its volume.

a. Endobronchial Valve (EBV) (Emphasys Medical Inc; Redwood City CA)²²

Table 2—Patient Selection Criteria for LVRS

Inclusion Criteria	Exclusion Criteria
Symptoms of emphysema refractory to medical treatment	Giant bullae > 5 cm
PULD by CT scan ^a	Bronchiectasis, sputum production > ½ cup/d
Evidence of airway obstruction by FEV ₁	Pulmonary hypertension
Evidence of hyperinflation by TLC and RV	PCO ₂ > 60 mm Hg
Abstinence from tobacco > 3 mo	Prednisone ≥ 20 mg/d
	NETT's "high risk for mortality" cohort
	Previous thoracotomy
	Extensive pleural disease
	High risk for thoracotomy
	Comorbidity; < 2-y life expectancy
	Unstable angina, CHF, MI < 6 mo; life-threatening cardiac arrhythmias

Commonly used inclusion/exclusion criteria for LVRS. CHF = congestive heart failure, MI = myocardial infarction; TLC = total lung capacity. See Table 1 for expansion of other abbreviations.

^aNETT and other groups also enrolled patients with homogeneous distribution of emphysema.

Table 3—NETT Outcome Categories From LVRS

Category	Baseline		Improvement		
	Anatomic Distribution	Exercise Tolerance	Function at 3 y	QOL at 4 y	Survival 5 y
1	PULD	Low	Yes <i>P</i> < .001	Yes <i>P</i> < .001	Yes <i>P</i> = .01
2	PULD	High	Yes <i>P</i> = .007	Yes <i>P</i> < .001	No
3	NPULD	Low	Yes	Yes <i>P</i> = .001	No
4	NPULD	High	No	No	No

LVRS outcome categories are based on anatomic distribution of emphysema and baseline exercise tolerance level. NPULD = non-PULD (includes predominant lower lobe, superior segment, and diffuse/homogenous disease); QOL = quality of life. See Table 1 for expansion of other abbreviations.

b. Intrabronchial Valve (IBV) (Spiration Inc; Redmond, WA)²³ (Fig 2)

2. Biologic Lung Volume Reduction (BioLVR) (Aeris Therapeutics, Inc; Woburn, MA) involves deployment of a biodegradable gel into subsegmental bronchi to collapse targeted hyperinflated pulmonary parenchyma and initiate an inflammatory response to selectively scar, shrink, and reduce the volume of treated lung.²⁴
3. Airway Bypass Tracts (ABT) (Broncus Inc; Mountain View, CA) achieved by creating extra anatomic fenestrations between hyperinflated pulmonary parenchyma and bronchial tree in order to allow escape of trapped gas and reduce lung volume.²⁵

None of the above four devices is approved by the FDA for treatment of emphysema in the United States; however, IBV and EBV received CE (Conformité Européenne) designation. Bronchoscopic Ther-

mal Vapor Ablation (Update Inc.; Seattle, WA) and nitinol self-actuating reduction coils (PneumRx Inc.; Mountain View, CA) are under development but available data are insufficient for meaningful evaluation of safety and efficacy.^{26,27}

Inclusion and exclusion criteria for BET strategies are similar to those used for LVRS (Table 2). EBV targeted PULD and PLLD, IBV was used only for PULD, and BioLVR was tested both in heterogenous and homogenous distribution of the disease, whereas the pivotal ABT trial enrolled only the homogenous phenotype of emphysema (Table 4).

ZEPHYR EBV

Zephyr EBV is a self-expanding nitinol stent with a silicon one-way duckbill valve that allows egress of gas and mucus during exhalation but bars entry of air during inhalation. EBV is available in sizes to fit subsegmental, segmental, and lobar bronchi. Valves can be removed or repositioned bronchoscopically.²²

During a nonrandomized 98-patient nine-center experience, a total of 396 EBV valves (4.04 ± 1.6 valves per patient) were deployed with a 90-day follow-up.²⁸ Improvements in FEV₁, FVC, residual volume (RV), and 6-min walk distance (6MWD) (Table 4) were significant without meeting Minimal Clinically Important Difference (MCID) levels.³⁶ Lobar targeting and the resultant lobar exclusion/collapse (LE) produced better results than sublobar treatment (Table 5). Data on QOL instruments were not reported. It is difficult to interpret these outcomes because of the short follow-up period and lack of uniform treatment strategies, such as unilateral vs bilateral treatment, complete vs partial lobar exclusion, and so forth.

There were eight (8%) serious complications, including one death. The less serious adverse events consisted of 17 COPD exacerbations, five pneumonias in nontreated lobes, and nine pneumothoraces

SURVIVAL AFTER LVRS¹¹

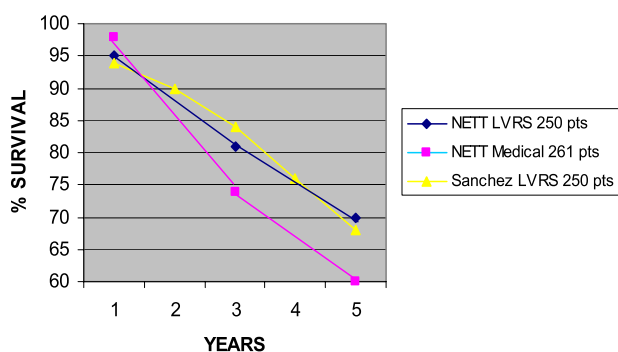


FIGURE 1. Five-year survival after LVRS. Survival curves for PULD emphysema reported from NETT's randomized data obtained under Freedom of Information Act⁷ and observational studies from Ciccone et al.⁶ Lower initial survivals of the surgical cohorts are due to operative mortality. The curves for the NETT's PULD group randomized to LVRS and observational heterogeneous LVRS populations from Ciccone et al.⁶ are essentially superimposable and reflect results superior to the NETT¹³ medically treated cohort. LVRS = lung volume reduction surgery; NETT = National Emphysema Treatment Trial; PULD = predominant upper lobe disease.

mostly associated with lobar collapse. In the ensuing EBV pivotal trial only one lung was targeted in order to prevent simultaneous collapse of both lungs.

The Endobronchial Valve for Emphysema Palliation Trial (VENT), a pivotal multicenter RCT (2:1 ratio of treated to control) with the Zephyr EBV valve, was completed in 2007 on 321 patients with heterogeneous emphysema. Upper or lower lobar, segmental, and subsegmental bronchi were unilaterally targeted.³⁷ Primary end points were changes in FEV₁ and 6MWD. In 214 treated patients, a total of 820 valves were inserted (median 4, range 1-9 per patient). During the procedure one or more valves were replaced or repositioned in 96 patients (45%) mostly because of unsatisfactory valve size or position. After correction of perceived shortcomings, the desired valve position was achieved in 95% of patients.

At the 6- and 12-month follow-ups, the treated cohort showed statistically significant improvement in FEV₁, 6MWD, and St. George Respiratory Questionnaire (SGRQ) compared with control subjects but failed to meet MCID criteria (Table 4). The functional

outcomes from VENT were less favorable than from the 98-patient EBV cohort study.³⁸

Within 1 year of treatment, valve-related complications included device malfunction (9.8%), pneumonia distal to the valve (4.2%), valve expectoration/migration (7.5%), and granulation tissue on the prosthesis (7%). CT scans after EBV deployment were available in 194 patients and showed satisfactory valve position in 109 (56.2%) patients but 85 (43.8%) exhibited malposition, expectoration, or other complications, of at least one valve. Moreover, only eight (28.6%) of the 28 participating clinical sites deployed all valves correctly, whereas 20 sites (71.4%) experienced varying degrees of technical failures.³⁹ A US Food and Drug Administration (FDA) panel convened on December 5, 2008, found Zephyr EBV “not approvable” but suggested further studies.²⁹ Subsequently Emphasys EBV was sold to Pulmonx Interventional Pulmonology, Palo Alto, CA. In an attempt to improve results Pulmonx introduced an endobronchial catheter-based device (Chartis System) for estimating collateral resistance and assist in selection of suitable patients for lung volume reduction.^{40,41}

Table 4—Bronchoscopic Emphysema Therapy Outcomes at 6 Months

Study	Patients, No.	FEV ₁ , %	FVC, %	RV, %	6MWD	RV/TLC, %	SGRQ, units
EBV							
Observational							
Heterogenous, ^{28,a} 3 mo	98	10.7 ± 26 ^b	9 ± 24 ^c	-4.9 ± 17 ^c	36.9 ± 90 m ^d
Randomized ^{29,e}							
VENT, hetero-unilateral							
EBV	220	5.8 ± 28 ^{f,g}	1.7% ± 30.3% ^{c,f}	...	-3.4 ^{c,f}
Control subjects	101	-0.6 ± 28.3	-4.0 ± 28.1	...	-2.6 ± 13.0
IBV, PULD							
Observational ^{30,31,a}	91	-3.4	...	0.06	3.4%-6.3%	...	-7.0 ^d
BioLVR							
Observational ^a							
PULD LD ³²	28	6.7 ± 12.9 ^c	5.1 ± 16.1	-7.1 ± 16.8	25.5 ± 53.2 m ^{c,f}	-4.2 ± 11.0	-6.9 ± 8.8 ^g
PULD HD	22	15.6 ± 16.8 ^g	9.1 ± 15.5 ^b	-9.0 ± 11.2 ^b	9.9 ± 51.2 m	-5.9 ± 8.2 ^c	-9.7 ± 18.8 ^g
Homogenous LD ³³	8	-11.1 ± 13.5 ⁱ	-6.0 ⁱ	...	-47.5 m	-0.1 ± 14.8 ⁱ	-4.6 ± 7.9
Homogenous HD	17	13.5 ± 20.1 ^e	9.3 ± 13.4 ^e	...	1.0	-5.0 ± 12.4 ⁱ	-11.4 ± 12.4 ^g
Unilateral, lobar ³⁴	12	25.9 ± 39.4 ⁱ	9.5	-5.3	39.9 m
Bilateral-subsegmental	9	13.2 ± 18.2	9.2	-3.9	8.9
ABT							
Observational ^{35,a}							
Homogenous							
RV/TLC > 0.67	18	4.1	17.8 ^c	-14 ^c	-1.0 m	...	-4.7
RV/TLC < 0.67	18	-3.6	-2.9	-0.4	-24.4 m	...	1.7

Results from the various types of bronchoscopic emphysema therapies calculated from mean values. ABT = airway bypass treatment; BioLVR = biologic lung volume reduction; EBV = EndoBronchial Valve; HD = high dose; IBV = IntraBronchial Valve; LD = low dose; MCID = minimal clinically important difference; VENT = Endobronchial Valve for Emphysema Palliation Trial. See Tables 1 and 2 for expansion of other abbreviations.

^aChange from baseline.

^bP ≤ .007.

^cP ≤ .025.

^dP ≤ .001.

^eP = .002.

^gDoes not meet MCID.

^hP ≤ .05.

ⁱNot significant.

Table 5—State of Lobar Fissure and Collapse/Exclusion Strategy

Study	Patients, No.	FEV ₁ , %		FVC, %		RV, %	6MWD, m	SGRQ, units
		3 mo	12 mo	6 mo	12 mo	6 mo	6 mo	6 mo
EBV								
Observational ²⁸								
Lobar exclusion	70	14.0 ± 29.3 ^a	...	9.7 ± 26.8	...	-4.5 ± 17	26.7 ± 59 ^b	...
Segment/subsegment	28	3.2 ± 15.7	...	7.4 ± 16.1	...	-5.7 ± 19.1	13.9 ± 46	...
Randomized ²⁹								
EBV-CFLE	33	21.4 ± 24.3 ^b	23.5 ± 25.9 ^b	9.9 ± 19.0 ^c	12.3 ± 23.2 ^c
EBV-No CFLE	118	2.4 ± 16.1	3.5 ± 18.8	2.2 ± 18.3	2.4 ± 18.5
IBV ³⁰								
Observational								
Atelectasis	6	0.14 ± 0.06	-0.7 ± 1.0	...	-15.3 ± 14
No atelectasis	66	-0.04 ± 0.16	0.1 ± 0.8	...	-7.3 ± 16
BioLVR, HD ³⁴								
Observational								
Unilateral, lobar	12	25.9 ± 39.4	...	9.5	...	-5.3	39.9	...
Bilateral, subsegmental	9	13.2 ± 18.2	...	9.2	...	-3.9	8.9	...

The effect (change from baseline) of complete lobar fissure and lobar targeting with various bronchoscopic emphysema treatments.

CFLE = complete fissure lobar targeting and exclusion. See Tables 1, 2, and 4 for expansion of other abbreviations.

^a*P* = .02.

^b*P* < .001.

^c*P* = .017.

IBV

The IBV is an umbrella-shaped, self-expanding device based on a similar unidirectional principle as its EBV counterpart (Fig 2). The valve is available in different sizes. Replacement or repositioning can be accomplished bronchoscopically.^{30,31} During a multicenter, nonrandomized, bilateral treatment trial on heterogeneous emphysema, a total of 609 valves (mean 6.7 valves per patient) were implanted in 91 patients. Segmental or subsegmental airways were targeted in 74% and 26%, respectively.^{30,42} Technical difficulties with valve implantation were encountered in two and pneumothorax occurred in nine patients, with one fatality. There was one nonfatal myocardial infarction and seven patients experienced bronchospasm. Migration, erosion, or expectoration of the valve and severe hemoptysis were not reported. Forty-four valves from 16 patients were removed for pneumonia, bronchospasm, COPD exacerbation, and pneumothorax.

At 6 and 12 months post-IBV implant, SGRQ improved but spirometry, lung volumes, and 6MWD did not change significantly (Table 4). No valve migration or expectoration was observed. CT scans showed no change in total lung capacity (TLC) but the volume of the targeted lobe decreased by approximately 10% in 87% of the subjects, whereas the volume of the nontreated territory increased by 11.0% in about 94% of the patients. The shifts in lobar volumes correlated with improvement in SGRQ (*P* < .01) and lung perfusion scans showed a shift of perfusion from the treated upper lobe to the nontreated lower lobe.

Spiration is presently conducting a double-blind, multicenter, randomized pivotal trial between bilateral IBV plus medical treatment and medical treatment alone on patients with PULD. Control subjects receive sham bronchoscopy. Primary efficacy end points are changes in SGRQ and lung volume on CT scan.

BioLVR

BioLVR involves deployment of a biodegradable gel into subsegmental bronchi in order to collapse targeted hyperinflated pulmonary parenchyma and stimulate an inflammatory response that scars and shrinks the treated lung. The biologic complex incorporates chondroitin sulfate and poly-L-lysine and is delivered in a fibrin vehicle simultaneously with a thrombin solution via a dual lumen catheter in the working channel of a flexible bronchoscope. The contents of the two lumens meet, mix, and polymerize at the target airway site and form the BioLVR gel. The liquid component of the gel presumably fills alveoli and blocks collateral ventilation. Safety and efficacy were demonstrated in a sheep emphysema model.²⁴

During a phase 2 non-RCT with PULD emphysema, 22 patients were treated with high-dose (HD = 20 mL/subsegment) and 28 with low-dose (LD = 10 mL/subsegment) BioLVR. The 6-month follow-up of 44 patients revealed greater improvement of FEV₁, FVC, and RV in the HD than in the LD cohorts. There was no significant change in 6MWD in either group (Table 4). At 6 weeks, CT scans showed localized scarring of treated sites in

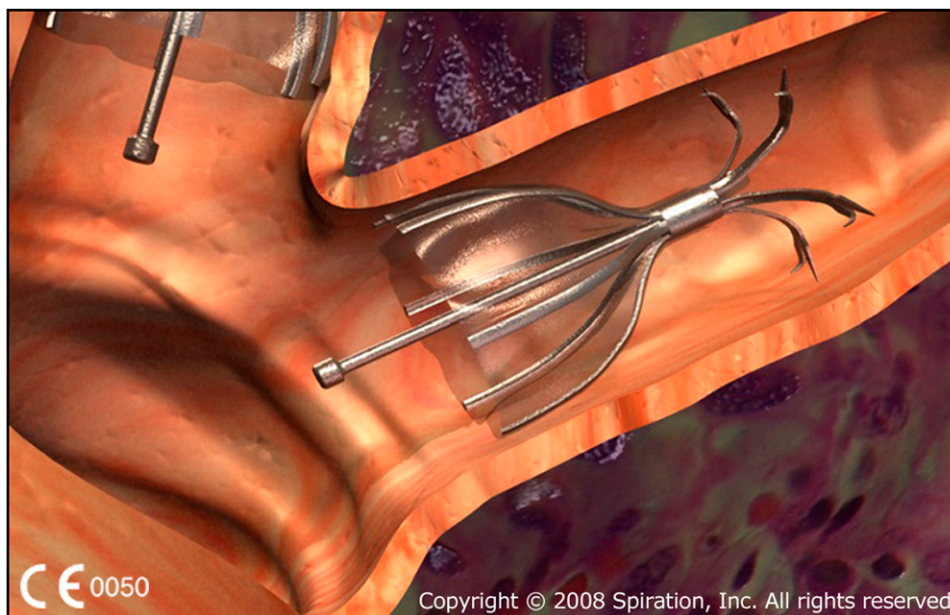


FIGURE 2. Schematic of an IntraBronchial valve in situ. Reprinted with permission from Spiration, Inc.

57% \pm 17% of LD and 68% \pm 20% of patients treated with HD BioLVR. The scarring at 6 months was sustained in the HD but not in the LD cohort. Radiologic evidence of scarring correlated with improvement in FEV₁.³²

In a study on bilateral treatment of homogenous emphysema, 17 patients received HD-BioLVR and eight patients received LD-BioLVR. At the 6-month follow-up, FEV₁, FVC, and RV/TLC improved in HD-BioLVR but not in the LD-BioLVR group. SGRQ improved in both arms of the study, but 6MWD improved in neither (Table 4).³³

In another HD BioLVR study on PULD, nine patients were treated at four subsegments in each of two upper lobes (bilateral-scattered), and 12 patients were treated at five to eight subsegments in one upper lobe (lobar-contiguous). Targeting a single lobe produced better results than an equal or larger dose delivered bilaterally into scattered subsegments of two lobes (Table 4).³⁴

BioLVR treatment was followed within 24 h, in >90% of patients, by a syndrome of fever, pleuritic pain, nausea, headache, malaise, and leukocytosis, consistent with an anticipated inflammatory response to the biologic materials introduced into the airways. The reaction subsided within 24 to 48 h. No deaths or device-related complications were reported.

On November 8, 2008, Aeris notified participating clinical sites that the company failed to come to an agreement with FDA on a phase 3 study design and that further testing was deferred. Subsequently the work on BioLVR was halted and feasibility studies on

a new product (Polymeric Lung Volume Reduction) were initiated.

INTERLOBAR FISSURE, TARGETING STRATEGY, AND EFFECTIVENESS OF BET

One year after EBV treatment in the VENT trial 33 of 151 subjects (21.9%) with available CT scans showed complete interlobar fissures and lobar exclusion/collapse (CFLE). These patients exhibited both improved spirometry and SGRQ. The 118 of 151 patients (78.1%) without CFLE experienced only improvement in SGRQ without favorable change in spirometry (Table 5).⁴³ In an IBV study lobar collapse was also associated with better symptomatic and physiologic response than sublobar or no collapse (Table 5).³⁰ However, lobar collapse was associated with an increased incidence of treatable pneumothorax. With BioLVR, unilateral lobar treatment showed better results than bilateral targeting with the same or higher dosage at scattered subsegments (Table 5).³⁴ Thus, it appears that by preventing cross-lobe collateral ventilation, complete lobar fissure facilitates more durable lobar collapse and effective lung volume reduction by unidirectional valves or BioLVR durable lobar collapse and effective lung volume reduction. This observation suggests that selection of patients with complete interlobar fissures would improve results from LVR. However, more data are needed to establish the reliability of assessment of the state of lobar fissures by CT imaging. The Chartis System may aid in estimating the degree of collateral

ventilation to regions of the lung under consideration for treatment with airway obstructive devices.^{41,42}

ABT

Choong and colleagues²⁵ hypothesized that creation of nonanatomic airways between hyperinflated pulmonary parenchyma and adjacent bronchi (ABT) would decompress hyperinflated lung and reduce its volume. The procedure is designed for homogenous emphysema and performed with a flexible fiberoptic bronchoscope as follows: (1) identification of blood vessels adjacent to planned sites of bronchial fenestration with a Mini Doppler Probe (Yield) in order to avoid vascular injury and bleeding, (2) fenestration of extraanatomic channels between bronchus and hyperinflated air spaces with a proprietary needle-balloon catheter (Yield), and (3) insertion of a paclitaxel-eluting stent (Exhale) to dilate the newly created channel and to maintain patency.

In 12 human lungs, explanted during lung transplantation for COPD, creation of three ABT channels increased FEV₁ from 245 ± 107 mL to 447 ± 199 mL ($P < .001$) and the addition of two more fenestrations to 666 ± 284 mL. ($P = .001$).⁴⁴ Animal studies 12 weeks after creation of stented ABT demonstrated patency rates of paclitaxel-eluting vs bare metal stents of 65% vs 0%.⁴⁵

In a 35-patient multicenter ABT pilot study on severe homogenous emphysema, a median of eight (range 2-12 per patient) stented fenestrations were created bilaterally, in upper and lower lobes.³⁵ A baseline RV/TLC > 0.67 was associated with improved FVC, TLC, RV, and SGRQ, but patients with RV/TLC ≤ 0.67 did not improve (Table 4). 6MWD and FEV₁ remained unchanged in both groups (Table 4). Bleeding during the procedure was controlled with topical epinephrine in all cases except for one patient who exsanguinated. Other complications included 12 COPD exacerbations, 10 respiratory infections, and two cases of pneumomediastinum. Six months after insertion 18 of 26 (69%) stents examined bronchoscopically were patent. Grgic and colleagues⁴⁶ reported that patency of the stents can be detected by multidetector CT scanning with a 94.7% sensitivity and 100% specificity.

Exhale Airway Stents for Emphysema is an FDA-approved double-blind multicenter pivotal trial on homogeneous emphysema and an RV/TLC of ≥ 0.65. Patients were randomized between ABT and sham bronchoscopy control in a ratio of 2:1. The primary end points are ≥ 12% improvement in FVC and ≥ 1-point reduction in modified Medical Research Council scale score. The study enrolled 315 patients. Preliminary reports indicate that 6 months after the

procedure the primary FEV₁ end point was not met but improvement in modified Medical Research Council score was statistically significant. At the 1-month follow-up, RV decreased by > 500 mL in approximately 40% of EBV-treated patients. However, characteristics of this favorable patient group and the duration of the improvement were not reported.⁴⁷

COMMENTS

A review of the published results from lung volume therapies for emphysema supports the following conclusions: First, observational and randomized studies provide compelling evidence that LVRS improves pulmonary function, exercise capacity, health-related QOL, and survival, especially in the PULD-low baseline exercise tolerance subset. The reasons for the apparent underuse of the procedure are not clear.

Second, the four extensively tested BET approaches are safer but far less effective than LVRS. Available data indicate IBV and BioLVR improve SGRQ values by MCID levels (> 4 units) and surpass the mean change of 3.5 SGRQ units reported from the large pharmaceutical trials with salmeterol/fluticasone in Towards a Revolution in COPD Health Study (TORCH) and tiotropium in Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT).^{48,49} IBV is also associated with decreased volumes in the treated and an increase in untreated regions of the lung on CT scan. These volume shifts correlate with improvement in SGRQ but without concomitant changes in lung function or exercise tolerance suggesting redirection of ventilation from treated to untreated areas. EBV and ABT did not meet primary end points on pivotal trials. ABT was followed by symptomatic and physiologic improvements in 40% of patients 1 month after treatment but the observed 31% stent closure at 6 months will probably prevent a sustained response. Based on pilot studies, BioLVR is associated with symptomatic and physiologic benefits. Although the physiologic changes do not reach MCID values, BioLVR has the promise of an effective bronchoscopic approach but further work was halted by the sponsor so that pivotal studies to verify the results probably will not be conducted. The physiologic improvements observed from the various bronchoscopic strategies to volume reduction do not reach MCID levels and longer-term follow-ups have not been reported. Although it is maintained that experienced bronchoscopists could perform the procedures without an intensive training, the frequent technical failures during deployment of EBV cast doubts on this claim. Third, a complete interlobar fissure facilitates lobar exclusion/collapse and may be instrumental in improved QOL and lung

function by both unidirectional valves and BioLVR (Table 5).

Fourth, midterm (1-3 years) durability and complications from the various BET strategies are not known. The relatively low complication rates combined with improvement in SGRQ and favorable lung volume shifts on CT scan suggest that IBV and EBV possess therapeutic potential. Predictors associated with symptomatic and physiologic improvements from ABT treatment have not been identified. In view of an anticipated relatively high stent closure rate, the duration of the improvement beyond 1 month remains to be seen.

The goal of any medical treatment is either to extend life span or to improve its quality, and ideally both. This principle is a basic tenet of medical therapeutics and forms the backbone of medical practice. Replacement of joints is a prime example of improving QOL without adding to longevity. Similarly, the majority of cardiac revascularization procedures palliate but do not extend survival. Palliation without lengthening life span is especially rewarding in debilitating diseases. The recent search for interventional treatment of advanced emphysema may have placed an undue emphasis on survival benefits without sufficient regard for the value of palliation. It would seem that a treatment modality with an acceptable low risk that provides palliation for at least 12 months could be viewed as therapeutic even without improvement in physiologic parameters.

Contrary to projections, it is apparent that the various BET approaches will cost more than originally estimated. Preliminary information indicates that most BET systems will cost \$12,000 to \$20,000 per procedure.

The continued search for safe and effective minimally invasive approaches to LVT will likely produce promising new methods. At present, however, no uniform system is available for assessing therapeutic merits of emerging strategies. A classification based on universally recognized variables would facilitate evidence-based evaluation of the clinical value of emerging BETs. The safety of a new device under consideration combined with the proposed efficacy grading can provide evidence-based risk/benefit information on clinical value (Table 6).

Sound health-care planning requires evidence-based estimates on use of emerging therapies. The number of patients who might benefit from LVRS or BET is highly controversial. Estimates range from the 254 operations performed between 2004 and 2005 to the projection by Make and Fein⁵⁰ that 1.35 million patients could benefit from LVRS. Weinstein reported that only 10% of patients referred to a tertiary care center for LVRS had the operation.⁵¹ NETT evaluated 3,997 patients, enrolled 1,218, and

only 511, or 12.7% of the 3,997 screened patients, had the favorable PULD distribution. Our retrospective analysis of 959 patients whose PFTs reflected Global Initiative for Chronic Obstructive Lung Disease stage 3 and 4 severity included 413 individuals a primary clinical diagnosis of emphysema and available CT scans. On the basis of current inclusion/exclusion criteria 15% of the 413 could be candidates for LVRS.⁵² This estimate is consistent with other reported data on the issue and appears to reflect a realistic projection of the size of population that could benefit from lung volume reduction.

In conclusion, the LVRS experience demonstrates convincingly that the principle of lung volume reduction is sound and the surgery is effective but associated with substantial mortality and morbidity. The ongoing search for a safe and effective BET has made significant strides and yielded partial success in some aspects. Although some presently available BLT devices are approved for use by European regulatory authorities, the available information does not warrant a recommendation for routine clinical use. Emerging bronchoscopic therapies for LVR may not quantitatively match the response obtained from LVRS, but even modest improvement over medical therapy, as assessed through an evidence-based, standardized, and multidimensional approach, would

Table 6—Classification for Evaluating Emerging Bronchoscopic Emphysema Treatments

Category	QOL	CT Scan	Exercise Tolerance	PFT	Survival (BODE)
0	NC	NC	NC	NC	NC
1	+	NC	NC	NC	NC
2	+	+	+	NC	NC
3	+	+	+	+	NC
4	+	+	+	+	+

Category 1 denotes subjective improvement measured by validated QOL instruments. The response is not corroborated by objective measures and without a randomized study cannot be distinguished from placebo effect. However, the symptomatic improvement represents palliation. Category 2 adds an objective dimension to the subjective response (ie, favorable volume changes on CT scan and/or improved exercise tolerance). Category 3: favorable category 1 and 2 responses are corroborated by improved lung function (RV, vital capacity, inspiratory capacity, and FEV₁) likely due to reduction in static and dynamic hyperinflation and improved lung recoil. Category 4 combines symptomatic and functional improvements with survival benefits. This response resembles the results by NETT from LVRS in PULD. BODE has been used as surrogate for survival in COPD and is especially helpful when only short-term follow-up is available. The changes in the variables for efficacy classification are of consequence only if they meet MICD levels that are attributable to BET under examination and only if sustained beyond 6-12 mo. + = improvement in MCID; BODE = body-mass index, obstruction (FEV₁), dyspnea (mMRC), and exercise tolerance (6MWD); Exercise Tolerance = CPET or 6MWD; NC = no change; PFT = pulmonary function test.

represent an advance in the treatment of severe emphysema.

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