Non-Medical Interventions for COPD

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Emphysema: Background

- Loss of lung tissue, particularly the alveolar septa
- Enlargement of alveolar airspaces with loss of elastic recoil of the lung
- Lung and thorax hyperinflation
- Compression of adjacent lung tissue
- Dynamic hyperinflation with more airway compression
- Dysfunction of chest cage mechanics and diaphragm
- Overload or dysfunction of respiratory and skeletal muscles

Lung Volume Reduction Surgery

- Lung volume reduction surgery (LVRS)
  - Removal of approximately 20-35% of the poorly functioning, space occupying lung tissue from each lung
  - Increased lung elastic recoil pressure
  - Improved expiratory flow rates
    - Improvement in FEV_1 and FVC
    - Decreased auto-PEEP and work of breathing
  - Decreased hyperinflation
    - Improved diaphragm function

Lung Volume Reduction Surgery

Lung Volume Reduction Surgery

- The National Emphysema Treatment Trial (NETT)
  - **Group 1:** Patients with predominantly upper lobe emphysema and low exercise capacity
    - Had improved survival, exercise capacity, and quality of life outcomes after LVRS compared to medical therapy
  - **Group 2:** Patients with predominantly upper lobe emphysema and high exercise capacity
    - Had improved exercise capacity and quality of life after LVRS but no difference in survival compared to medical therapy
  - **Group 3:** Patients with non-upper lobe emphysema and low exercise capacity
    - Had improved quality of life after LVRS but no difference in survival or exercise capacity compared to medical therapy
  - **Group 4:** Patients with non-upper lobe emphysema and high-exercise capacity
    - Had decreased survival after LVRS with no change in exercise capacity or quality of life compared to medical therapy
  - Low exercise capacity $\leq$ 40 W for men and $\leq$ 25 W for women on CPET

Lung Volume Reduction Surgery

- Good Candidates
  - Have stopped smoking for at least 4 months
  - Have disabling emphysema despite complete compliance with optimum medical therapy
  - Must be able to participate in a pulmonary rehabilitation program prior to and after surgery
  - Other medical conditions must be well controlled and must not present unacceptable risks for complications from the procedure
  - Must have a pattern of emphysema that is amenable to surgical management
    - There are space occupying, poorly functioning areas of the lung which can be removed to improve lung function
      - Chest x-ray, CT scan, and lung perfusion studies

Lung Volume Reduction Surgery

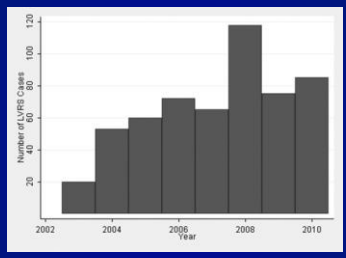
- Poor Candidates
  - Patients with non-upper lobe emphysema and high exercise capacity
  - Patients with extremely poor pulmonary function (FEV1 ≤ 20% predicted) and either homogenous distribution of emphysema on CT scan or extremely poor carbon monoxide diffusing capacity (DLCO ≤ 20% predicted)

LVRS Potential Complications

- Prolonged air leakage is the most common complication after LVRS
- Air leaks with a median 7-day duration have also been reported in 90% of patients
- Intraoperative complications (9%)
- Postoperative complications (50%)
  - Pneumonia (18.2%) can occur in emphysema patients, especially in patients who have a history of recurrent bouts
  - Reintubation (21.8%)
  - Arrhythmias (18.6%)
  - Bleeding (2-5%)
  - Death: The chance of dying after LVRS is approximately 3-8%

Lessons learned from the National Emphysema Treatment Trial. Ann Thorac Surg 2006; 82:197

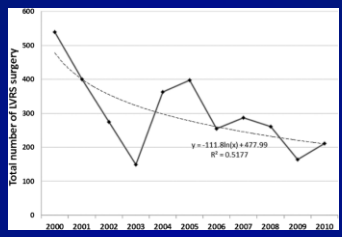
LVRS Utilization



Yearly annual volume of LVRS reported in the STS Database from January 2003 to December 2010

Marquita R. Decker MR et al, Lung volume reduction surgery since the National Emphysema Treatment Trial: study of Society of Thoracic Surgeons database. J Thorac Cardiovasc Surg 2014; 148:2651.

LVRS Utilization



- National Trends in Lung Volume Reduction Surgery in the United States: 2000 to 2010
- Nationwide Inpatient Sample (NIS) database search
- Administrative dataset created by the Agency for Healthcare Research and Quality that contains data from all community hospitals in the United States

Ahmad S. Chest. 2014;146:e228-e229.

Bronchoscopic Lung Volume Reduction: Background

- Dyspnea and subjective symptom improvement in majority of patients
- Function: PFT and exercise
  - FEV_1 average improvement of 50-70% (0.7 to 1.1 L)
  - About 2/3 of patients have improvement
- Survival advantage with surgery in certain subgroups, but with 5+% mortality and 20-50% morbidity
- Can bronchoscopic lung volume reduction techniques achieve results similar to surgical LVRS?
- Bronchoscopic lung volume reduction would obviate surgical morbidity and mortality
  - 90 day mortality 5.2% in NETT excluding high risk group

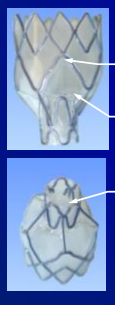
Bronchoscopic Treatment of Emphysema

- One way valves
- Biologic lung volume reduction
- Steam thermal ablation
- Coils

Endobronchial Valves

- Allows gas to vent during inspiration
- Prevents air entry during inspiration
- Two potential anatomic responses
  - Target area collapses: improved lung mechanics similar to LVRS
  - Target area does not collapse: valve blocks inspiratory ventilation to poorly perfused emphysematous lung improving V/Q matching
  - Either response would decrease dynamic hyperinflation

Pulmonx Zephyr Endobronchial Valve (EBV)



EBV Design

Self-expanding retainer and seal
- stabilizes device in airway using two linked rings and anti-migration
- Webbing creates closed cells with redundant contact points to ensure adequate seal against the bronchial wall

One-way valve
- Blocks air during inspiration, allows venting of trapped air during expiration
- allows mucus clearance

EBV Procedure Overview

Advance housing into target segment, confirm sizing using gages

Confirm Zephyr EBV positioning and sizing

Zephyr EBV allowing air to exit from during expiration

Zephyr EBV preventing air from entering during inspiration

VENT

*Endobronchial **V**alve for **E**mphysema PalliatioN **T**rial*

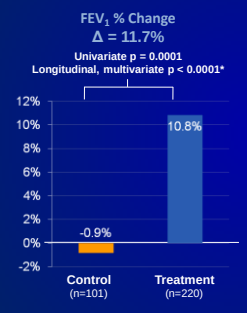
emphasys medical, inc.

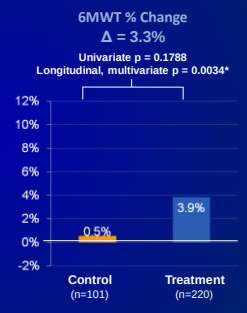
Trial Design

- Bronchoscopic lung volume reduction versus optimal medical management
- Patient population-heterogeneous emphysema
- Multicenter, randomized, prospective trial
- 2:1 treatment:control allocation ratio
- Unilateral valve placement in most emphysematous lobe
- Complete lobar exclusion performed
- Intention to treat analysis
- 321 patients enrolled

Sciurba FC et al. New Engl J Med 2010; 363:1233

Co-Primary Endpoints - 12 months

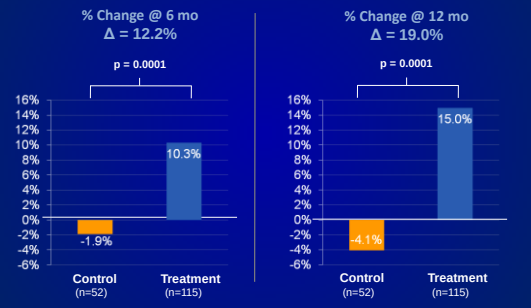




*By interaction with heterogeneity

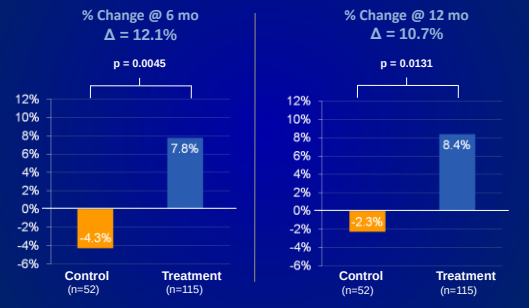
Sciurba FC et al. New Engl J Med 2010; 363:1233

FEV1: High Heterogeneity Group



Sciurba FC et al. New Engl J Med 2010; 363:1233

6MWT: High Heterogeneity Group

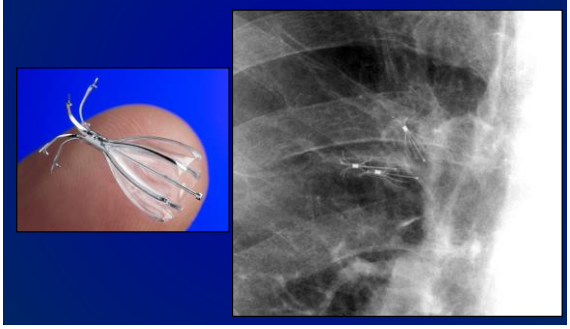


Sciurba FC et al. New Engl J Med 2010; 363:1233

Pulmonx Zephyr Endobronchial Valve (EBV)

- Initial pivotal study results were not sufficient for FDA approval
- Device is approved for use in Europe
- Additional study is being conducted in the US

Olympus/Spiration IBV Valve



Intrabronchial Valve (IBV)

Trial Design

- Bronchoscopic lung volume reduction versus optimal medical management
- Patient population-heterogeneous emphysema
- Multicenter, randomized, sham controlled, prospective trial
- 1:1 treatment:control allocation ratio
- Bilateral upper lobe valve placement
- Complete lobar exclusion was not performed
- Intention to treat analysis
- 277 patients enrolled

Wood et al. J Bronchol Intervent Pulmonol 2014: 21:288

Olympus/Spiration IBV Valve

TABLE 2. Primary Composite Effectiveness Measure and Individual Components of Quantitative CT Volumes and SGRQ (Baseline to 6 mo)

Responders	Treatment Group (N = 142)	Control Group (N = 135)	Difference (Treatment – Control) 95% BCI
Composite measure			
SGRQ and NUL and UL	6/121 (5.0%)	1/134 (0.7%)	0.048%, 9.212%*
CT volume (mL)			
UL (# < 0, %)	−224 ± 299 (98/120, 82)	−17 ± 204 (71/133, 53)	−272, −14*
NUL (# ≥ 10%, %)	214 ± 384 (34/120, 28)	−27 ± 292 (12/133, 9)	155, 326*
SGRQ			
Mean change	+2.15 ± 16.36	−1.41 ± 11.26	0.04, 7.07*
Responders ≥ −4, (%)	39/121 (32.2)	53/133 (39.8)	−19.0%, 4.2%

*Statistically significant.
BCI indicates Bayesian credible interval; CT, computed tomography; NUL, non–upper lobe; SGRQ, St. George's Respiratory Questionnaire; UL, upper lobe.

Wood et al. J Bronchol Intervent Pulmonol 2014: 21:288

Olympus/Spiration IBV Valve

	Treatment Group (N = 142)			Control Group (N = 135)			Difference (Treatment – Control)
	Obs	Mean	SD	Obs	Mean	SD	95% BCI
FEV_1 (L)	118	−0.07	0.17	132	0.00	0.16	(−0.11, −0.02)*
FEV_1% predicted	118	−2.11	5.49	132	0.04	5.74	(−3.56, −0.74)*
FVC (L)	118	−0.28	0.46	132	0.00	0.43	(−0.39, −0.17)*
FVC % predicted	118	−7.26	11.37	132	0.30	12.80	(−10.60, −4.54)*
TLC (L)	118	0.04	0.82	131	−0.09	1.27	(−0.13, 0.40)
TLC % predicted	118	0.54	14.67	131	−0.89	24.97	(−3.65, 6.50)
RV (L)	118	0.31	1.00	131	−0.07	1.29	(0.09, 0.67)*
RV % predicted	118	12.57	51.11	131	−4.24	64.70	(2.26, 31.34)*
Prescribed O_2 (L/min)	121	0.13	0.83	134	0.15	0.66	(−0.21, 0.17)
PO_2 (mm Hg)	110	−1.76	8.91	125	−1.28	8.46	(−2.73, 1.77)
PCO_2 (mm Hg)	114	2.10	4.47	128	0.62	4.20	(0.38, 2.59)*
6-minute walk test (m)	120	−24.02	69.81	133	−3.40	76.63	(−38.84, −2.44)*
MMRC	119	−0.24	1.02	133	−0.14	1.00	(−0.35, 0.16)
SF-36 PF	109	0.90	20.81	132	2.53	17.38	(−6.58, 3.31)
SF-36 PCS	108	0.11	7.94	130	0.73	7.53	(−2.63, 1.37)

*Statistically significant.
BCI indicates Bayesian credible interval.

Wood et al. J Bronchol Intervent Pulmonol 2014: 21:288

IBV Valve (Olympus/Spiration)

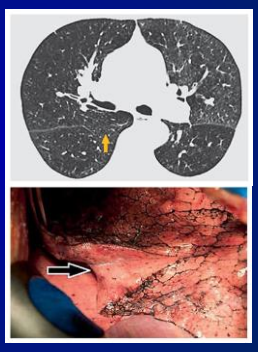
- Pivotal study in the US failed to achieve end-points
- Is approved for use for prolonged air leaks following pulmonary resection

Collateral Ventilation

- Analysis of the initial endobronchial valve studies have revealed that collateral ventilation is a significant issue for treatment failure
- Collaterals
  - Pores of Kohn
    - Apertures in the alveolar septae
    - Function primarily as pathways for alveolar lining fluid
  - Canals of Lambert
    - Tubular communications between distal bronchioles and adjacent alveoli
    - Collateral ventilation of primary lobules
  - Channels of Martin
    - Communications between terminal bronchioles from adjacent lung segments

Collateral Ventilation

- In the case of BLVR, however, not the interlobular but the interlobar CV is considered responsible for the failure of valve treatment
- Surgery as well CT studies have established fusion of adjacent lobes (parenchymal bridges)
- In one study left major fissure was incomplete in 43% and the right major fissure in 48%



Aziz et al. J Thorac Imaging 2004: 19:186

Collateral Ventilation

- Incomplete fissures are suggestive of CV
- In post-hoc analysis of VENT and Eur-VENT studies showed that patients with complete lobar fissures had better outcomes following BLVR
- CV may also be assessed bronchoscopically with the Chartis system

TABLE 2 Clinical outcomes at 6 and 12 months in endobronchial valve (EBV)-treated and control patients stratified by computed tomography fissure integrity

	Complete fissure			Incomplete fissure		
	EBV	Control[#]	p-value	EBV	Control	p-value
Patients n	44	19		67	40	
Δ FEV_1 %						
6 months	16±21	2±14	0.02	1±18	-1±21	0.7
12 months	15±29	-2±22	0.04	0±23	-2±19	0.6
Δ 6MWD %						
6 months	11±34	19±54	0.6	7 ±36	2±19	0.4
12 months	13±35	10±44	0.8	5±30	0 ±34	0.5
Δ cycle work-load W						
6 months	4±14	-3±7	0.03	0±14	-3±11	0.4
12 months	4±14	-2±9	0.10	-2±13	-6±13	0.2
Δ SGRQ points						
6 months	-6±15	3±15	0.09	-4±14	-1±14	0.2
12 months	0±15	4±11	0.4	-1±14	-1±14	0.9
Lost to follow-up	7 (16)	0		6 (9)	2 (5)	
Died	2 (5)	1 (5)		4 (6)	3 (8)	

Herth FJ et al. Eur Respir J 2012: 39:1334
Hert FJ et al. Eur Respir J 2013: 41:302

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation

STELVIO Trial

Trial Design

- Bronchoscopic lung volume reduction with Zephr valve versus optimal medical management
- Patient population-heterogeneous or homogeneous emphysema
  - FEV1 < 60%, TLC > 100%, RV > 150%
- Multicenter, randomized, prospective trial
- 1:1 treatment:control allocation ratio
- Excluded if had incomplete fissure on HRCT
- Also excluded if had CV assessed via Chartis
- Unilateral valve placement in most emphysematous lobe
- Complete lobar exclusion performed
- Intention to treat analysis
- 68 patients randomized

Klooster K et al. New Engl J Med 2015; 373:2325

STELVIO Trial

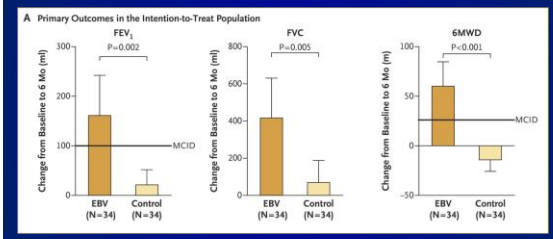
Table 2. **Mean Change from Baseline to 6 Months of Follow-up in Primary Efficacy Outcomes in the Intention-to-Treat Population.***

Variable	EBV Group (N=34)	Control Group (N=34)	Between-Group Difference	P Value
Change in FEV_1				
Milliliters (95% CI)	161 (80 to 242)	21 (−9 to 52)	140 (55 to 225)	0.002
Percentage (95% CI)	20.9 (11.1 to 30.7)	3.1 (−0.4 to 6.6)	17.8 (7.6 to 28.0)	0.001
Response rate — %	59	24	—	0.003
Change in FVC				
Milliliters (95% CI)	416 (201 to 631)	69 (−50 to 187)	347 (107 to 588)	0.005
Percentage (95% CI)	18.3 (9.3 to 27.3)	4.0 (−0.7 to 8.6)	14.4 (4.4 to 24.3)	0.005
Change in distance on 6-min walk test				
Meters (95% CI)	60 (35 to 85)	−14 (−25 to −3)	74 (47 to 100)	<0.001
Percentage (95% CI)	19.6 (10.4 to 28.9)	−3.6 (−6.9 to −0.4)	23.3 (13.6 to 32.9)	<0.001
Response rate — %	59	6	—	<0.001

* Paired t-tests were used to calculate within-group mean differences in changes from baseline to 6 months, P values, and 95% confidence intervals. Two-sample t-tests or, in the absence of a normal distribution, Wilcoxon signed-rank tests were used to calculate between-group mean differences, P values, and 95% confidence intervals. Fisher's exact test was used to calculate the between-group difference in response rates. Response rates were calculated by counting the number of patients for whom the change at 6 months met or exceeded the minimal clinically important difference for FEV_1 (>10%)[12] and the 6-minute walk test (>26 m).[11]

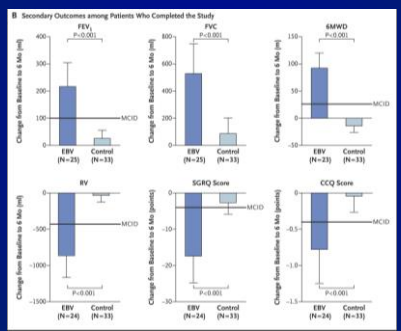
Klooster K et al. New Engl J Med 2015; 373:2325

STELVIO Trial



Klooster K et al. New Engl J Med 2015; 373:2325

STELVIO Trial



Klooster K et al. New Engl J Med 2015; 373:2325

STELVIO Trial

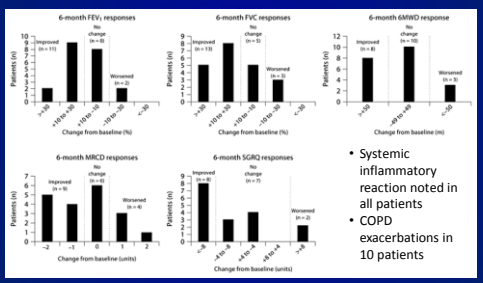
Table 3. **Serious Adverse Events during 6 Months of Follow-up.***

Event	EBV Group (N=34)	Control Group (N=34)	P Value†
	no. (%)		
Total no. of serious events	23	5	<0.001
Pulmonary events			
Death	1 (3)‡	0	1.00
COPD exacerbation with hospitalization	4 (12)	2 (6)	0.67
Pneumonia	2 (6)	1 (3)	1.00
Pneumothorax	6 (18)	0	0.02
Resolved ≤14 days after onset, without drainage	1 (3)	0	1.00
Resolved ≤14 days after onset, with drainage	2 (6)	0	0.49
Required temporary valve removal	1 (3)§	NA	NA
Required permanent valve removal because of recurrent pneumothorax	1 (3)	NA	NA
Required permanent valve removal, after temporary removal and reimplantation, because of recurrent pneumothorax	1 (3)	NA	NA
Other EBV-related events requiring permanent removal of all valves			
Torsion of the bronchus	2 (6)¶	NA	NA
Pneumonia distal to valve	1 (3)‖	NA	NA
Increased sputum, dyspnea, or coughing without patient-perceived treatment benefit	2 (6)	NA	NA
Other EBV-related events requiring valve replacement			
Valve migration	2 (6)	NA	NA
Valve expectoration	0	NA	NA
Valve dislocation due to formation of granulation tissue	1 (3)	NA	NA
Increased sputum, dyspnea, or coughing	1 (3)	NA	NA
Stroke	1 (3)	2 (6)	1.00

Lung Sealant BLVR

- AeriSeal-Aeris Therapeutics
- Bronchoscopic injection of hydrogel that seals and collapses lung
- Subsequent inflammatory response that induces scarring and leads to lung volume reduction
- Atelectatic portion of lung cannot re-expand because both main airways and collateral ventilation channels are filled with hydrogel

Lung Sealant

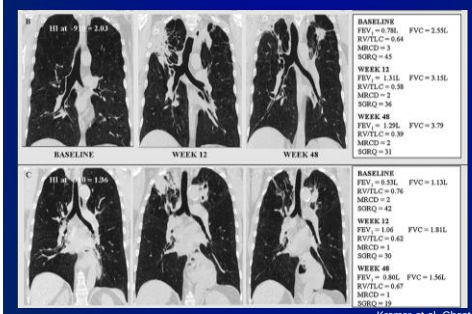


- Systemic inflammatory reaction noted in all patients
- COPD exacerbations in 10 patients

- 25 patients with heterogeneous emphysema
- Treated single lobe up to 6 sites, 1-2 procedures

Herth et al. Respiration 2011; 82:36

Lung Sealant BLVR



- FEV1 increased by 510 mL
- FVC increased by 1240 mL
- RV/TLC decreased by 39%
- SGRQ decreased by 14 points

- FEV1 increased by 270 mL
- FVC increased by 430 mL
- RV/TLC decreased by 12%
- SGRQ decreased by 23 points

Kramer et al. Chest 2012; 142:1111

ASPIRE Trial Design

- Bronchoscopic lung volume reduction with AeriSeal versus optimal medical management
- Patient population-upper lobe predominant heterogeneous emphysema
  - FEV1 < 50%, TLC > 100%, RV > 150%
- Multicenter, randomized, prospective trial
- 1:1 treatment:control allocation ratio
- Bilateral upper lobe sub-segmental treatment in a single session
- Intention to treat analysis
- 57 patients randomized-34 treatment and 23 control
- Study terminated due to lack of funding

Come et al. Eur Respir J 2015; 46:651

ASPIRE Trial

TABLE 2 Proportion of patients achieving minimally clinically important differences in measured variables

	3 months			6 months		
	Treatment	Control	p-value	Treatment	Control	p-value
Subjects n	34	23		21	13	
FEV1#	47.1	8.7	0.001	52.4	15.4	0.068
SGRQ¶	58.8	47.8	0.414	76.2	46.2	0.159
mMRC+	55.9	26.1	0.026	52.4	38.5	0.664
6MWD§	NA	NA	NA	52.4	0	0.0025

Come et al. Eur Respir J 2015; 46:651

Aspire Trial

TABLE 3 Serious adverse events

	0–30 days Patients (events)		31–60 days Patients (events)		61–90 days Patients (events)		>90 days Patients (events)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Death			1 (1)		1 (1)			
Respiratory failure#	3 (3)		1 (1)					
Pneumonia	2 (3)		6 (7)		4 (5)		3 (3)	2 (2)
COPD exacerbation	5 (5)	2 (2)	1 (1)	1 (2)	1 (1)		4 (6)	1 (1)
PAIR	4 (5)		1 (1)					
Pneumothorax	1 (2)							
Lung cavity							1 (1)	
Lung mass								1 (1)
Dyspnoea	1 (1)							

PAIR=post-treatment acute inflammatory response

Come et al. Eur Respir J 2015; 46:651

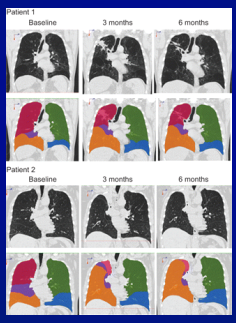
Lung Sealant BLVR

- Aeris Therapeutics has terminated US studies
- Intellectual property acquired by PulmonX

Thermal Vapor Ablation

- Uptake Medical
- Steam induces inflammatory response on proximal airways and distal lung parenchyma
- Inflammatory response generates atelectasis and subsequent scarring with lung volume reduction
- Effect should be independent of presence of interlobar collateral ventilation

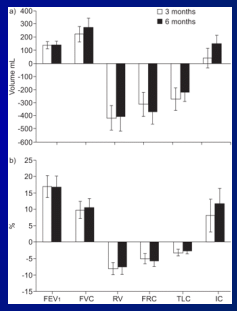
Thermal Vapor Ablation



Snell et al. Eur Respir J 2012; 39:1326

Thermal Vapor Ablation

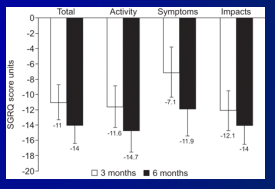
- 44 patients
- Heterogeneous emphysema
- Treatment of single upper lobe
- Average lobe volume loss from baseline was 718 mL at 3 months and 716 mL at 6 months, a 48% reduction in lobar volume
- 55% of subjects had an FEV1 improvement ≥12% at 6 months and 58% had an improvement in FEV1 of ≥100 mL
- Average change in 6MWD was 24 m and 47 m at 3 and 6 months



Snell et al. Eur Respir J 2012; 39:1326

Thermal Vapor Ablation

- Mean improvement in SGRQ total score was 11 and 14 points at 3 and 6 months, respectively
- 57% and 73% of subjects had a clinically meaningful improvement (decrease) in the SGRQ total score of ≥4 points at 3 and 6 months
- Total of 29 serious adverse events were reported in 19 subjects
  - COPD exacerbation in 9
  - Pneumonia in 6
  - Lower respiratory tract infection in 4
  - Hemoptysis in 3



Snell et al. Eur Respir J 2012; 39:1326

Thermal Vapor Ablation

- STEP-UP multicenter study completed but not published
- Per report FEV1 improved by 14.7% and SGRQ improved
- Device CE approved

Lung Volume Reduction Coil

- Nitinol wire pre-formed into a coil shape
- Creates mechanical lung volume reduction after implantation
- Increases the recoil properties of the treated lung tissue
- Should be unaffected by collateral ventilation
- Typically 10 coils placed in the most emphysematous lobe

RePneu coil-PneumRx

LVRC: Mechanism of Action

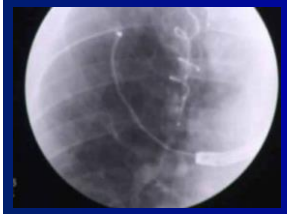
- The LVRC is designed to re-tension the airway network and compress diseased tissue in the emphysematous lung
  - Re-tensioning reduces airway collapse and air trapping
  - Does not block airways (valves/sealant) or induce fibrosis (lung sealant)
- Proposed Benefits of this mechanical approach include
  - Independence from collateral ventilation
  - Airway tethering
  - Restoration of elastic recoil
  - Gentle, well-tolerated Nitinol implant
- The Coil's designed mechanism of action seeks to restore the lung's natural elastic recoil and radial airway suspension

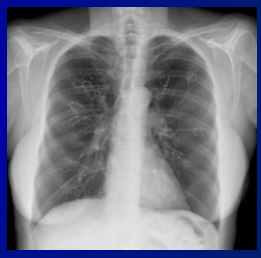
Lung Volume Reduction Coil

- Bronchoscopically deployed into bronchus as straight low-profile devices in emphysematous regions of lung
- Placement is controlled by clinician using simple guidance delivery system
- When desired placement is achieved, implant is allowed to resume its coil shape

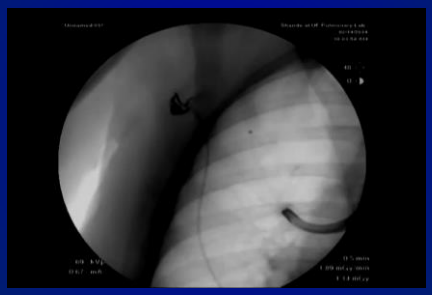
Herth et al. Eur Respir J 2009: 35:A1829

Lung Volume Reduction Coil





Lung Volume Reduction Coil



Lung Volume Reduction Coil

Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomised controlled trial

Pallav L Shah, Zaid Zoumot, Suveer Singh, Stephen R Bicknell, Ewen T Ross, John Quining, Nicholas S Hopkinson, Samuel V Kemp, for the RESET trial Study Group

- 47 patients with severe heterogeneous or homogeneous emphysema
- Randomized study of coil placement (n=23) or usual medical care (n=24)
- Median number of coils 18.5
- 21 patients had bilateral treatment and 2 had unilateral treatment

Shah et al. Lancet Resp Med 2013; 1:233

Lung Volume Reduction Coil

	Treatment (n= 23)	Usual care (n= 23)	Between-group difference in change from baseline*	p value
Primary outcome				
St George's Respiratory Questionnaire	−8·11 (−13·83 to −2·39)	0·25 (−5·58 to 6·07)	−8·36 (−16·24 to −0·47)	0·04
Secondary outcome				
Total lung capacity (L)	−0·24 (−0·38 to −0·10)	−0·13 (−0·27 to 0·01)	−0·11 (−0·29 to 0·07)	0·22
Residual volume (L)	−0·51 (−0·73 to −0·30)	−0·20 (−0·42 to 0·02)	−0·31 (−0·59 to −0·04)	0·03
6-min walk test (m)	51·15 (27·65 to 74·66)	−12·39 (−36·61 to 11·83)	63·55 (32·57 to 94·53)	<0·001
% change in FEV_1	14·19 (6·84 to 21·55)	3·57 (−4·02 to 11·17)	10·62 (1·12 to 20·12)	0·03
mMRC dyspnoea score	−0·24 (−0·57 to 0·09)	−0·09 (−0·44 to 0·26)	−0·15 (−0·60 to 0·30)	0·5

Data are mean change from baseline (95% CI). FEV_1=forced expiratory volume in 1 s. *Corrected for difference between groups at baseline.

Table 2: Primary and secondary efficacy outcomes* in the intention-to-treat population (change from baseline at 90 days after final treatment)

Shah et al. Lancet Resp Med 2013; 1:233

Lung Volume Reduction Coil

	Treatment (n= 23)	Usual care (n= 23)	p value*
Primary outcome			
SGRQ ≥4-point improvement	15 (65%)	5 (22%)	0·01
SGRQ ≥8-point improvement	13 (57%)	3 (13%)	0·01
Secondary outcome			
Respiratory volume: 0·35-L reduction	13 (57%)	4 (17%)	0·01
6-min walk test: 26-m improvement	17 (74%)	4 (17%)	<0·0003
FEV_1: 10% improvement	13 (57%)	6 (26%)	0·07

Data are n (%). *Fisher's Exact Test. SGRQ=St George's Respiratory Questionnaire. FEV_1= forced expiratory volume in 1 s.

Table 3: Responder analysis of primary and secondary efficacy outcomes in the intent-to-treat population (change from baseline at 90 days after final treatment)

Shah et al. Lancet Resp Med 2013; 1:233

Lung Volume Reduction Coil

	Treatment (23 patients, 44 procedures)			Usual care (23 patients)			p value‡
	Events (n)*	Patients (n)	Incidence (%)†	Events (n)	Patients (n)	Incidence (%)†	
Treatment recovery periods§							
Device removal	0	0	0%	0	0	0%	NA
Exacerbation	2	2	5%	1	1	4%	>0·99
Haemoptysis	0	0	0%	0	0	0%	NA
Lower respiratory tract infection¶	2	2	5%	0	0	0%	0·49
Pneumothorax	2	2	5%	0	0	0%	0·49
Respiratory failure	0	0	0%	0	0	0%	NA
Total	6	6	15%	1	1	4%	0·02

Shah et al. Lancet Resp Med 2013; 1:233

Lung Volume Reduction Coil

Lung volume reduction coil treatment for patients with severe emphysema: a European multicentre trial

- 60 patients with severe heterogeneous emphysema
  - Interestingly many patients had homogeneous emphysema when quantitative CT software analysis was performed
- Open label study, 11 centers
- Median of 10 coils per lung
- 55 patients had bilateral treatment and 5 had unilateral treatment

Deslee et al. Thorax 2014; 69:980

Lung Volume Reduction Coil

Table 4 Efficacy results at 6 and 12 months

	6 Months Overall group (N=58)	6 Months 12-month follow-up group (N=34)	12 Months 12-month follow-up group (N=34)
FEV_1, L	+0.11±0.20 (n=54, p<0.001)	+0.12±0.28 (n=33, p=0.021)	+0.11±0.30 (n=34, p=0.037)
FEV_1, % pred (% change)	+15.36±26.68 (n=54, p<0.001)	+17.81±31.71 (n=33, p=0.003)	+16.04±35.54 (n=34, p=0.017)
FVC, L	+0.20±0.53 (n=54, p=0.008)	+0.33±0.57 (n=33, p=0.002)	+0.28±0.45 (n=34, p=0.001)
RV, L	−0.65±0.90 (n=58, p<0.001)	−0.80±1.03 (n=34, p<0.001)	−0.71±0.81 (n=34, p<0.001)
RV, % pred (% change)	−11.31±15.25 (n=58, p<0.001)	−14.38±15.42 (n=34, p<0.001)	−13.75±12.65 (n=34, p<0.001)
RV/TLC	−4.51±12.19 (n=58, p=0.007)	−6.06±8.58 (n=34, p<0.001)	−3.12±15.59 (n=34, p=0.245)
6MWD, m	+29.7±74.1 (n=56, p=0.004)	+42.4±73.5 (n=34, p=0.002)	+51.4±76.1 (n=32, p=0.003)
SGRQ, points	−12.1±12.9 (n=56, p<0.001)	−10.4±15.8 (n=33, p<0.001)	−11.1±13.3 (n=32, p<0.001)
mMRC, points	−0.6±1.2 (n=58, p<0.001)	0.8±0.9 (n=34, p<0.001)	−0.7±0.8 (n=34, p<0.001)

Efficacy at 6 months for all LVR coil treatments (n=58, overall group) and at 6 and 12 months (n=34, 12-month follow-up group columns). Results are given as change from baseline. Data are shown as mean±SD.
Data in parentheses are the numbers of actual measurements available per variable tested followed by the actual p value.
6MWD, 6-min walking distance; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified Medical Research Council dyspnoea score; RV, residual volume; SGRQ, St George's Respiratory Questionnaire total score; TLC, total lung capacity.

Deslee et al. Thorax 2014; 69:980

Lung Volume Reduction Coil

Table 5 Responder rates at 6 and 12 months

Variable	MCID	6 months (%)	12 months (%)
FEV_1	≥12%[11]	48.0	40.6
RV	≥0.35[12]	64.8	57.6
6MWD	≥26 m[13]	52.8	60.0
SGRQ	≥4 points[14]	74.1	65.6
SGRQ	≥8 points	61.1	53.1

Responder rates at 6 and 12 months after bilateral lung volume reduction coil treatment using minimal clinically important differences (MCID) for forced expiratory volume in 1 s (FEV_1), residual volume (RV), 6-min walking distance (6MWD) and the St George's Respiratory Questionnaire total score (SGRQ). Results are given as percentage of responders to total patients.

Deslee et al. Thorax 2014; 69:980

Lung Volume Reduction Coil

Table 6 Results at 12 months after bilateral LVR coil treatment for patients classified as heterogeneous and homogeneous emphysema

	Visual CT assessment* (12 month follow-up group)			Digital CT assessment* (12 month follow-up group)		
	Heterogeneous (n=20)	Homogeneous (n=13)	p Value	Heterogeneous (n=16)	Homogeneous (n=17)	p Value
ΔFEV$_1$, L	+0.14±0.30	+0.08±0.28	0.585	+0.18±0.32	+0.05±0.26	0.220
ΔRV, L	−0.69±0.87	−0.68±0.46	0.859	−0.75±0.78	−0.66±0.72	0.719
Δ6MWD, m	+53.9±65.1	+46.0±67.9	0.739	+74.9±67.4	+27.9±57.8	0.049
ΔSGRQ, points	−12.9±15.1	−7.3±8.7	0.187	−12.4±13.9	−9.1±12.9	0.491

Results are given as mean±SD change from baseline. Heterogeneity and homogeneity were assessed by both a visual CT assessment (a 4-point qualitative score of the degree of tissue destruction where a difference of ≤1 point for both lungs was regarded as homogeneous) and a digital CT assessment (where the software calculated the percentage area of destruction at −950 Hounsfield Units; a difference of ≤25% in destruction for both lungs was regarded as homogeneous).
6MWD, 6-min walking distance; FEV$_1$, forced expiratory volume in 1 s; LVR, lung volume reduction; RV, residual volume; SGRQ, St George's Respiratory Questionnaire total score.
*p<0.05 for all end-points compared to baseline.

Lung Volume Reduction Coil

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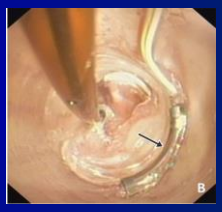
*p<0.05 for all end-points compared to baseline.

Deslee et al. Thorax 2014; 69:980

Targeted Lung Denervation

- Holaira
- Ablative therapy that targets the parasympathomimetic innervation of the airways and simulates the effect of anticholinergic drugs
- Radiofrequency catheter is advanced bronchoscopically into the main bronchus
- Energy of 15 to 20 W is delivered to ablate the parasympathetic pulmonary nerves along the main bronchi



Targeted Lung Denervation

- Prospective, multicenter feasibility trial in Europe
- 15 patients with COPD were enrolled
- All patients were treated bilaterally by TLD at 10 W in a single procedure
- At baseline off tiotropium, FEV1 and 6MWT distance 0.77 L & 354 m
- At baseline on tiotriopium FEV1 1.09 L & 6MWT 406 m
- 90 days following TLD off tiotropium FEV1 1.02 L & 6 MWT 409 m

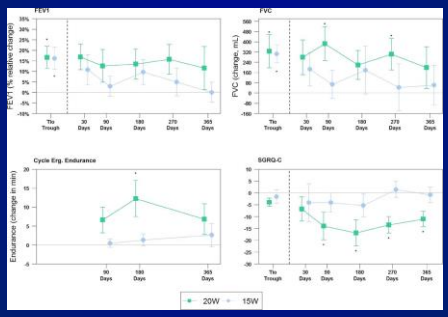
Valipour A et al. Abstract 1775; ERS 2014

Targeted Lung Denervation

- Multicenter feasibility study
- 22 patients (10 at 15 W, 12 at 20 W)
- FEV1 30%–60% of predicted, 15% or greater relative increase in FEV1 following inhalation of 80 µg ipratropium bromide
- Bronchial perforation not requiring treatment in 2 patients and COPD exacerbation in 1 patient

Slebos et al. Thorax online 2015

Targeted Lung Denervation



Slebos et al. Thorax online 2015

DISCUSSION