Bronchoscopic Volume Reduction for Severe Emphysema

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Theoretical Etiology of LVR(S) Associated Improvement

- Lowering of operating lung volumes
  - Improves respiratory muscle function and mechanics
- Mitigation of dynamic hyperinflation
- Improved elastic recoil
- Improved lung – chest wall dynamics

[1] Sciurba et al. NEJM 1996;334:1095-1099.
[2] Gelb AF et al.. Am J Respir Crit Care Med 1996; 154:945-951.
[3] Fessler HE and Permutt S.. Am J Respir Crit Care Med 1998; 157:715-722.
[4] Gelb AF et al. CHEST 1998; 113:1497-1506.

LVRS Advantages

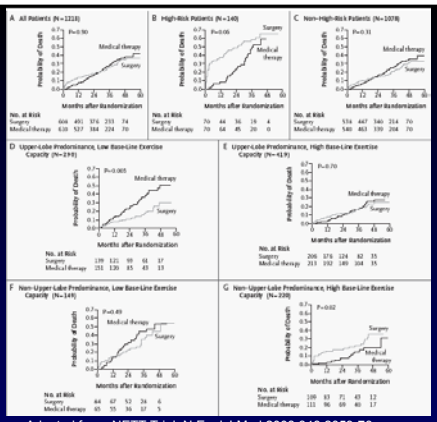
- Exercise capacity improvements
  - 16% LVRS vs. 3% controls
- Improvements in HRQOL
  - OR 5.06
- Improvements in pulmonary function
  - 65% had improvement in FEV1

NETT Trial. N Engl J Med 2003;348:2059-73.

LVRS – Disadvantages

- 90-day Mortality
  - 7.9% (5.2% in non-high risk group) treatment vs. 1.3% medical therapy[1]
  - 2.9% predominantly upper lobe disease[1]
- Morbidity
  - 7% Reoperation Rate (3% for persistent air leak, 1% for bleeding)[2]
  - 22-28% still hospitalized at 30 days (vs. 2.2% in medical treatment group)[2,1]

[1] NETT Trial. N Engl J Med 2003;348:2059-73.
[2] Yusen, et al. *Chest*. 2003;123:1026-1037



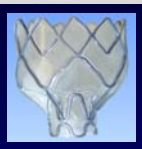
Adapted from NETT Trial. N Engl J Med 2003;348:2059-73.

Non-LVRS Approaches to Volume Reduction

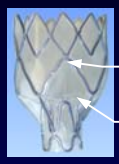
- Compression/banding devices
- Endobronchial sealants
- Endobronchial sealants/plugs
- Endobronchial fenestration with bypass
- Endobronchial valves
  - Spiration valve (IBV valve)
  - Emphasys valve (Zephyr)

Endobronchial Valves

- IBV – Spiration Valve
  - Published animal studies
  - Recently finished human safety studies
- Emphasys Zephyr
  - Published pilot human safety and efficacy studies
  - Ongoing FDA pivotal trials



Emphasys 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

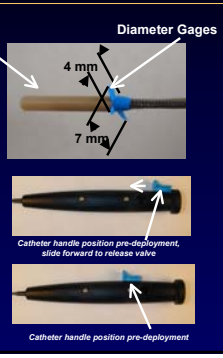
Catheter Delivery System

Delivery

- Through the Scope delivery of catheter to target bronchial segment
- Ergonomic control handle for steering and deployment
- Works with flexible bronchoscope with ≥2.8mm working channel

Deployment

- Valve compressed and retained in housing
- Positioned at target site, sizing verified using diameter gages
- Housing retracted via catheter handle releasing valve



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

Emphasys Valve Studies

Toma study - pilot safety

Yim study – pilot efficacy

[1] Toma TP et al. Bronchoscopic volume reduction with valve implants in patients with severe emphysema. Lancet 2003; 361:931-33

[2] Yim, et al. Early results of endoscopic lung volume reduction for emphysema. J Thor Cardiovasc Surg 2004; 127:1564-73

Toma, et al
Inclusion/Exclusion

INCLUSION
- Diagnosis of emphysema
- Severe exertional dyspnea despite six weeks rehab

EXCLUSION
- Lower lobe distribution or solitary bullae
- FEV1 < 10% pred
- PCO2 > 55mmHg
- Current smokers
- AAT deficiency
- Chronic sputum production
- Age >75

Toma, et al

Population Characteristics

- 8 patients
- Median FEV1 0.79L (24% pred)
- Mean RV 273% pred
- Mean DLCO 35% pred
- Mean pO2 75mmHg
- 4 patients RUL, 2 LUL, 2 LUL + lingula

Toma, et al

Results

- FEV1
  - Median increase 36% (*P* = .028)
- DLCO
  - Median increase 29% (*P* = .017)
- Shuttle distance
  - No significant change
- 25% (2/8) pneumothorax rate
- NO pneumonias noted

Toma, et al

Results

- 4/8 patients exhibited atelectasis
  - Showed greatest improvement in FEV1
- Patients without atelectasis exhibited improvements in FEV1
  - ? Due to improved V/Q ratios?

Yim, et al

Inclusion/Exclusion

Inclusion criteria

- Symptomatic emphysema
- Age 50 to 80 y
- Patient has shortness of breath on routine daily activities despite maximal medical therapy
- Heterogeneous disease on pulmonary CT and V/Q scan

Exclusion criteria

- FEV1 20% of predicted value
- Hypercapnea with PaCO2 55 mm Hg
- Diffusion capacity 25% of predicted value
- Pulmonary hypertension
- Evidence of active pulmonary infection
- Patient cannot or will not comply with follow-upinvestigations

Yim, et al

Baseline Characteristics

- 20 Patients
- One to two lobes
  - 2 to 8 valves
- Mostly upper lobe targets
- Bilateral 8 of 20
- Mean FEV1 0.73L (33% pred)
- Mean 6MWD 251m

Yim, et al

Results

- FEV1 Improvement
  - 15% at 30 days
  - 26% at 90 days (*P* = .009)
- 6MWD Improvement
  - 22% at 30 days (*P* = .012)
  - 28% at 90 days (*P* = .003)
- QOL Improvement
  - 7of 9 domains in SF-36 improved at 30- and 90-days (*P* < .001)
  - Significant improvement in all 4 domains of SGQL at 90 days (*P* = .012 to < .001)

Spirometric functional changes before and after Emphasys bronchial valve placement

Variable	Before procedure	At 1 mo	At 3 mo	Repeated-measures analysis: *P* value	Repeated-measures analysis: Linear trend	*P* value (with Bonferroni correction): Comparison between before procedure and at 1 mo	*P* value (with Bonferroni correction): Comparison between before procedure and at 3 mo
Pulmonary function							
FEV_1 (L)	0.73 ± 0.26	0.84 ± 0.27	0.92 ± 0.34	.003	.006	.075	.009
FEV_1 (% predicted)	33.3 ± 11.9	38.8 ± 13.2	42.2 ± 15.0	.004	.004	.045	.006
FVC (L)	1.94 ± 0.62	2.12 ± 0.47	2.25 ± 0.61	.002	.002	.06	.015
FVC (% predicted)	63.3 ± 17.6	70.5 ± 14.3	73.9 ± 17.1	<.001	.002	.021	.012
TLC (L)	7.03 ± 1.60	6.50 ± 1.77	6.58 ± 1.48	.895	.930	1.041	1.446
TLC (% predicted)	146.4 ± 30.8	144.6 ± 60.9	141.1 ± 40.4	.860	.869	1.263	2.16
DLCO (mL/min/mm Hg)	8.00 ± 4.13	9.18 ± 4.12	9.06 ± 4.09	.504	.339	1.677	1.179
DLCO (% predicted)	50.8 ± 21.0	59.6 ± 22.0	60.6 ± 24.4	.157	.133	.54	.426
RV (L)	4.98 ± 1.49	4.85 ± 1.97	4.43 ± 1.43	.851	.770	1.065	1.14
RV (% predicted)	368.9 ± 127.4	360.9 ± 191.2	326.7 ± 133.9	.876	.987	1.332	1.539
RV/TLC	0.71 ± 0.12	0.72 ± 0.13	0.67 ± 0.10	.699	.565	1.392	.885
Exercise tolerance							
6MWD (m)	251.6 ± 100.2	306.3 ± 112.3	322.3 ± 129.7	<.001	<.001	.012	.003

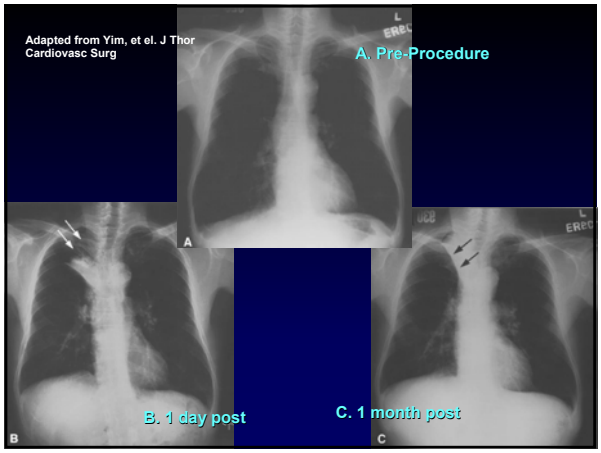
Data are presented as mean ± SD. FEV_1, Forced expiratory volume in 1 second; *FVC*, forced vital capacity; *TLC*, total lung capacity; *DLCO*, carbon monoxide–diffusing capacity; *RV*, residual volume; 6MWD, 6-min walking distance.

Yim, et al. J Thor Cardiovasc Surg 2004; 127:1564-73

Health-related quality of life changes before and after Emphasys bronchial valve placement

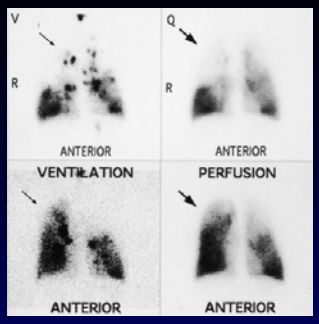
Variable	Before procedure	At 1 mo	At 3 mo	Repeated-measures analysis: *P* value	Repeated-measures analysis: Linear trend	*P* value (with Bonferroni correction): Comparison between before procedure and at 1 mo	*P* value (with Bonferroni correction): Comparison between before procedure and at 3 mo
SF-36*							
Physical functioning	30.5 ± 16.6	57.5 ± 27.0	63.1 ± 32.0	<.001	<.001	<.001	.003
Role limitation due to physical problems	36.8 ± 41.1	65.6 ± 40.7	56.9 ± 46.8	.090	.095	.288	.378
Bodily pain	94.7 ± 14.7	89.8 ± 20.6	92.9 ± 20.8	.189	.808	1.725	1.152
General health	32.5 ± 15.0	61.9 ± 21.6	44.7 ± 26.0	<.001	.012	<.001	.243
Vitality	44.2 ± 21.0	64.4 ± 14.8	60.0 ± 27.2	.005	.013	.015	.357
Social functioning	48.7 ± 30.6	69.5 ± 26.2	71.5 ± 39.3	.004	.002	.123	.123
Role limitation due to emotional problems	70.2 ± 44.3	85.4 ± 32.1	70.4 ± 45.6	.400	.348	.654	2.415
Mental health	69.3 ± 17.4	79.5 ± 14.5	76.4 ± 22.4	.042	.042	.114	.822
Change in health	38.9 ± 17.0	85.0 ± 21.3	74.4 ± 28.9	<.001	<.001	<.001	<.001
SGRQ†							
Symptoms score	52.8 ± 17.1	N/A	39.2 ± 27.4	N/A		N/A	.025
Activity score	78.8 ± 16.4	N/A	52.8 ± 28.2	N/A		N/A	<.001
Impact score	56.7 ± 20.7	N/A	31.8 ± 26.4	N/A		N/A	.014
Total score	62.7 ± 14.2	N/A	39.3 ± 24.4	N/A		N/A	.003
MRC grade‡	3 (2–5)	2 (1–5)	1 (1–4)	N/A		.006	.003

Yim, et al. J Thor Cardiovasc Surg 2004; 127:1564-73



Yim, et al
Radiographic Changes

- 10/23 lobes (43%) revealed some degree of collapse up to 90 days post-treatment
  - 20% re-expanded over follow-up period
  - 20% developed during course of follow-up
- 4/20 (20%) developed PTX
  - Chest tubes placed in 3 due to large size
  - 1/3 had air leak after tube placed



Bilateral upper lobe valve placements

Adapted from Yim, et el. J Thor Cardiovasc Surg

Yim, et al
Other Complications

- 2/20 had mild CO2 retention
- NO pneumonia
- Mean hospital stay 5.6 days

VENT Overview

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

Emphasys

The Endobronchial Valve (EBV) Concept

- Implantable one-way valve
- Through the Scope delivery technique
- Blocks inspiratory flow to diseased lung regions
- Reduces hyperinflation
- Re-directs airflow to healthier lung areas

→

- Improved breathing mechanics
- Physiologic and clinical improvement

Potential benefits of LVRS, but with a minimally invasive & potentially reversible approach

EBV Clinical Experience

Patients:
- Over 140 patients treated
- Over 320 valves implanted
- Over 30 patient 1 year+ post implant

Preliminary Results:
- Significant improvements in lung function and exercise tolerance
- Results in publication[1,2,3]

Based on results, embarking upon pivotal clinical trial

[1]Toma, Geddes, et al. Bronchoscopic volume reduction with valve implants in patients with severe emphysema. *Lancet* 2002; 361: 931-33
[2]Yim, et al. Early results of endoscopic lung volume reduction for emphysema. *J Thorac Cardiovasc Surg* 2004; 127: 1564-73
[3]Snell, et al. The potential for bronchoscopic lung volume reduction using bronchial prostheses. *Chest* 2003; 124: 1073-1080

VENT Study Design

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

Design	- Multi-center - Randomized 2:1 (treatment:control) - Optimal Medical Mgmt + EBV vs. Optimal Medical Mgmt.
Measured Endpoints	- Physiologic: spirometry, plethysmography, DLCO - Clinical: exercise tolerance, QOL, oxygen usage - Safety
Follow-up	- 2-3 day, 7-10 day, 1 mo, 3 mo, 6 mo, 12 mo

Trial Design - Inclusion / Exclusion

	Inclusion	Exclusion
General	• 40 to 75 years of age • BMI ≤31.1 kg/m2 (men) BMI ≤ 32.3 kg/m2 (women) • Nonsmoking for 4 months prior • Plasma continine level < 13.7 ng/ml • No child bearing potential OR a negative pregnancy test	• Unplanned weight loss >10% usual or low body weight • Active fever/infection • Alpha-1 antitrypsin deficiency • Currently enrolled in other trial
Exercise Tolerance	• Post rehabilitation 6-min walk of > 140m	• Unable to complete 3 minutes unloaded peddling on cycle ergometer

Trial Design - Inclusion/Exclusion

	Inclusion	Exclusion
Emphysema Distribution	• Heterogeneous emphysema based on HCRT	• Unsuitable disease distribution by HRCT (severe, homogeneous) • Evidence of large bullae in non-target lobe (Encompassing >30% of either lung)
COPD Status	• Stable with < 20 mg prednisone (or equivalent) qd	• History of recurrent respiratory infections (>1 hospitalization in last year) • Clinically significant sputum production (>4 tablespoon per day (>60 ml per day)) • Clinically significant bronchiectasis
Lung Function	• FEV1 > 45% predicted • TLC > 100% predicted • RV > 150% predicted • PaCO2 < 50mm Hg *(Denver, Colorado < 55 mm Hg)* • PaO2 > 45 mm Hg *(Denver, Colorado > 30 mm Hg) on room air*	• FEV1 < 15% predicted value • DLCO < 20% predicted value

Trial Design - Inclusion/Exclusion

	Inclusion	Exclusion
Cardiovascular Status	*(none)*	• CHF or MI within 6 mo and LVEF < 45% • History of exercise-related syncope • Resting bradycardia (< 50 beats/min), frequent multifocal PVCs, complex ventricular arrhythmia, sustained SVT • Dysrhythmia that may pose risk during exercise / training
Other Disease	*(none)*	• Pleural or interstitial disease that precludes surgery • Pulmonary nodule requiring surgery • Clinical suspicion or proven history of pulmonary hypertension • Evidence or history of Cor Pulmonale • Prior lung transplant, LVRS, med. sternotomy, lobectomy • Systemic disease or neoplasia compromising survival • Concomitant disease or condition interfering with trial

Study Design - Patient Flow

SCREEN 1	- Informed consent, medical history, vital signs, physical exam, record oxygen usage
SCREEN 2	- Spirometry, plethysmography, DLCO, exercise tolerance, blood work, HRCT, ECG
PULM REHAB	- 6-8 week pulmonary rehab
BASELINE WORKUP	- Spirometry, plethysmography, DLCO, exercise tolerance, blood work, chest X-ray, ECG, QOL
RANDOMIZE	- Randomize (2:1)
TREAT CONTROL	- Treatment or control arm office visit
FOLLOW - UP	- PFT, 6MWT, QOL, imaging, etc. depending on time point - 2-3 day, 7-10 day, 1 mo, 3 mo, 6 mo, 12 mo

VENT US Sites

St. Vincent's (Cicenia)
NY Presbyterian (Maxfield)
Beth Israel (Ernst)
U. of Pittsburgh (Sciurba)
U. Iowa (McLennan)
MUSC (Strange)
Hopital Calmette (Marquette)
Topeka Pulmonary (Leeds)
Sarasota Memorial (Voelker)
Tulane U. (Kovitz)
S. Illinois U. (Hazelrigg
VA Houston (Goodnight-White)
UC Davis (Chan)

Temple (Criner)
U. of Maryland (Krasna)
Baptist Memorial (Golden)
Botsford Hospital (Ferguson)
McGuire (Moses)
Mayo Clinic (Edell)
Remington-Davis (Cordasco)
U. Kentucky (Zgoda)
Shands / U. Florida (Jantz)
Charite Campus Mitte (Witt)
Pulmonary Associates (Levine)
Bay Area Chest (Freilich)
VA Tucson (Campbell)
Wayne State (Simonoff)