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

Emphysema: Background

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 FEV₁ 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 < 40 W for men and < 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 homogeneous 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%)
  - 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


Bronchoscopic Lung Volume Reduction: Background

- Dyspnea and subjective symptom improvement in majority of patients
- Function: PFT and exercise
  - FEV1 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 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 Valve for Emphysema Palliation Trial

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

Co-Primary Endpoints - 12 months

- **FEV1 % Change**
  - Δ = 11.7%
  - Univariate p = 0.0001
  - Longitudinal, multivariate p < 0.0001

- **6MWT % Change**
  - Δ = 3.3%
  - Univariate p = 0.1788
  - Longitudinal, multivariate p = 0.0034

*By interaction with heterogeneity*
FEV1: High Heterogeneity Group

<table>
<thead>
<tr>
<th></th>
<th>Control (n=52)</th>
<th>Treatment (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Change @ 6 mo</td>
<td>10.3%</td>
<td>4.1%</td>
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<tr>
<td>Δ</td>
<td>12.2%</td>
<td>0%</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.0001</td>
<td>0.0021</td>
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</table>


6MWT: High Heterogeneity Group

<table>
<thead>
<tr>
<th></th>
<th>Control (n=52)</th>
<th>Treatment (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Change @ 6 mo</td>
<td>7.8%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Δ</td>
<td>12.1%</td>
<td>10.7%</td>
</tr>
<tr>
<td>p</td>
<td>0.0045</td>
<td>0.0131</td>
</tr>
</tbody>
</table>


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

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
IBV Valve (Olympus/Spiration)

- Pivotal study in the US failed to achieve endpoints
- 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
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

Table 1. Mean Change from Baseline to 6 Months of Follow-up in Primary Efficacy Outcomes in the Intention-to-Treat Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>EBV Group (n=34)</th>
<th>Control Group (n=34)</th>
<th>Between-Group Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in FEV1 (%)</td>
<td>-1.6 (18.9)</td>
<td>-1.6 (18.6)</td>
<td>-0.0 (24.3)</td>
<td>0.999</td>
</tr>
<tr>
<td>Percentage (%)</td>
<td>38.1 (33.5)</td>
<td>35.7 (30.1)</td>
<td>2.4 (5.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>47 (28)</td>
<td>48 (28)</td>
<td>1 (2)</td>
<td>0.999</td>
</tr>
<tr>
<td>Change in FVC (%)</td>
<td>1.2 (0.1)</td>
<td>0.7 (0.3)</td>
<td>0.5 (0.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Percentage (%)</td>
<td>36.6 (31.0)</td>
<td>35.7 (27.7)</td>
<td>0.9 (3.3)</td>
<td>0.999</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>47.0 (24.4)</td>
<td>48.9 (24.4)</td>
<td>1.9 (1.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in distance on 4-min walk test</td>
<td>80 (128)</td>
<td>84 (128)</td>
<td>-4 (128)</td>
<td>0.999</td>
</tr>
<tr>
<td>Change in dyspnea score (%)</td>
<td>3 (11)</td>
<td>3 (11)</td>
<td>0 (9)</td>
<td>0.999</td>
</tr>
<tr>
<td>Change in air trapping (%)</td>
<td>0.1 (0.9)</td>
<td>0.1 (0.9)</td>
<td>0 (0.9)</td>
<td>0.999</td>
</tr>
</tbody>
</table>

* Fixed effects were used to calculate within-group mean differences in changes from baseline to 6 months. P values, and 95% confidence intervals, for two-sample t-tests or, in the absence of a normal distribution, non-parametric tests were used to calculate between-group differences. Tests were performed to evaluate the primary group difference for each efficacy outcome. Bonferroni correction was applied to account for the number of tests. Change from baseline in change of EBV and FVC was adjusted with trend analysis of the proportional change of the baseline value. *p* < 0.05.

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

STELVIO Trial

A. Primary Outcomes in the Intention-to-Treat Population

B. Secondary Outcomes among Patients Who Completed the Study
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

Herth et al. Respiration 2011; 82:36

25 patients with heterogeneous emphysema
Treated single lobe up to 6 sites, 1-2 procedures
Systemic inflammatory reaction noted in all patients
COPD exacerbations in 10 patients

Kramer et al. Chest 2012; 142:1111

Lung Sealant BLVR

Herth et al. Respiration 2011; 82:36

Lung Sealant

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>
<thead>
<tr>
<th>Subjects</th>
<th>3 months</th>
<th>6 months</th>
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<tbody>
<tr>
<td>Treatment</td>
<td>Control</td>
<td>p-value</td>
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<tr>
<td>34</td>
<td>23</td>
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<tr>
<td>FVC (%)</td>
<td>47.1</td>
<td>8.7</td>
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<tr>
<td>mNTFIC</td>
<td>58.8</td>
<td>47.8</td>
</tr>
<tr>
<td>mNTFIC</td>
<td>15.9</td>
<td>25.1</td>
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<tr>
<td>PGs</td>
<td>NA</td>
<td>NA</td>
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Come et al. Eur Respir J 2015; 46:651

Aspire Trial

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

PAIR=post-treatment acute inflammatory response
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

- 44 patients
- Heterogeneous emphysema
- Treatment of single upper lobe
- Average lobe volume loss from baseline was 716 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

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

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

**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

**Lung Volume Reduction Coil**

- 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
• 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
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 bronchi
  Energy of 15 to 20 W is delivered to ablate the parasympathetic pulmonary nerves along the main bronchi

Results are given as mean ± standard deviation. Lung volume and CT were assessed by chest CT 12 months after TLD in 15 patients enrolled at 15 W. The difference of mean bronchiolar diameters before and after TLD are depicted in Table 6. A significant difference of mean bronchiolar diameters before and after TLD depicted the percentage of lung volume decrease. The percentage of lung volume decrease depicted Table 6. The difference of mean bronchiolar diameters before and after TLD is depicted in Table 6. All patients were treated bilaterally by TLD at 10 W in a single procedure off tiotropium. FEV1 and 6MWT distance 0.77 L & 354 m. FEV1 1.09 L & 6MWT 406 m. 90 days following TLD off tiotropium FEV1 1.02 L & 6MWT 409 m. Lung Volume Reduction Coil

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 tiotropium FEV1 1.09 L & 6MWT 406 m
• 90 days following TLD off tiotropium FEV1 1.02 L & 6MWT 409 m

Slebos et al. Thorax online 2015

Deslee et al. Thorax 2014; 69:980

Valipour A et al. Abstract 1775; ERS 2014

Slebos et al. Thorax online 2015
DISCUSSION