Emphysema Disease Background

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Emphysema Affects ~3.5 Million Americans\(^a\)

- A subset of COPD
- Abnormal and permanent enlargement of lung air spaces distal to the terminal bronchiole
- Caused by irreversible destruction of alveolar walls
- Damaged alveoli lead to air trapping and hyperinflation

\(^a\) CDC FastStats. [https://www.cdc.gov/nchs/fastats/copd.htm](https://www.cdc.gov/nchs/fastats/copd.htm).

The Clinical Picture of Emphysema

- Breathlessness
- Cough
- Wheezing
- Loss of weight
- Barrel chest
- Sleep problems
- Lung infections

Emphysema and Lung Hyperinflation

- Hyperinflation is a devastating and common complication of emphysema

Progressive Air Trapping and Hyperinflation Leads to Decreased Inspiratory Capacity

Breathlessness/Dyspnea Caused by Hyperinflation Leads to Significant Morbidity and Poor Survival

- Decreased exercise performance
- Impaired respiratory muscle and chest wall mechanics
- Decreased quality of life
- Prolonged respiratory failure requiring mechanical ventilation
- Increased mortality

Adapted from Global Initiative For Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of COPD. http://goldcopd.org
Hyperinflation Is Associated With Poor Prognosis

Emphysema Staging

**GOLD Staging System**

- **Stage 1:** Very mild emphysema with FEV$_1$ about 80% or more of normal
- **Stage 2:** Moderate emphysema with FEV$_1$ between 50% and 80% of normal
- **Stage 3:** Severe emphysema with FEV$_1$ between 30% and 50% of normal
- **Stage 4:** Very severe emphysema with FEV$_1$ < 30% of normal

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Overall Survival in NHANES III Stratified by Lung Function Impairment (6,261 Participants Age ≥50 yr)

Disease Characteristics of Emphysema

Heterogeneous

Upper lobe

Lower lobe
(basal segment)

Homogeneous

With patchy areas

Completely homogeneous

### Key Clinical Parameters in the Assessment of Emphysema

<table>
<thead>
<tr>
<th>Measure/Endpoint</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td><strong>Lung Function</strong></td>
<td></td>
</tr>
<tr>
<td>FEV(_1)</td>
<td>Forced Expiratory Volume in 1 Second</td>
</tr>
<tr>
<td>RV</td>
<td>Residual Volume</td>
</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td></td>
</tr>
<tr>
<td>SGRQ</td>
<td>St. George’s Respiratory Questionnaire</td>
</tr>
<tr>
<td><strong>Exercise Capacity</strong></td>
<td></td>
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<tr>
<td>6MWT</td>
<td>6-Minute Walk Test</td>
</tr>
</tbody>
</table>
Natural History of Severe Emphysema
Data From NETT Control Group Over 2 Years

Worsening of all clinical outcomes over time

FEV₁

Mean change from baseline, % predicted

SGRQ

Mean change from baseline, points

6MWT

Mean change from baseline, meters

-0.7 -0.6 -0.5 -0.4 -0.3 -0.2 -0.1 0 0.1 0.2 0.3 0.4 0.5 0.6 0.7

6 12 24 Months

NETT=National Emphysema Treatment Trial.
St. George Respiratory Questionnaire Assesses Breathlessness With Activity (Question 11)

Breathlessness adversely impacts quality of life and limits activities of daily living

<table>
<thead>
<tr>
<th>I don’t feel out of breath doing these activities</th>
<th>I do feel out of breath doing these activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting or lying still</td>
<td>Walking or dressing yourself</td>
</tr>
<tr>
<td>Washing or dressing yourself</td>
<td>Walking around the house</td>
</tr>
<tr>
<td>Walking outside on level ground</td>
<td>Walking up a flight of stairs</td>
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<tr>
<td>Walking up hills</td>
<td>Playing sports or other physical activities</td>
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</tbody>
</table>
# Available Treatment Options Have Limitations in Severe Emphysema

<table>
<thead>
<tr>
<th>Pharmacotherapy (SAMA, SABA, LAMA, LABA, ICS PDE-4 inhibitors)</th>
<th>Lung volume reduction surgery (LVRS)</th>
<th>Lung transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient population</strong></td>
<td>GOLD 3 and 4</td>
<td>Selected patients with GOLD 4</td>
</tr>
<tr>
<td>All emphysema patients</td>
<td>Severe hyperinflation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No large bulla</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Upper lobe emphysema</td>
<td></td>
</tr>
<tr>
<td><strong>Level of evidence</strong>a</td>
<td>Level A</td>
<td>Level C</td>
</tr>
<tr>
<td><strong>Benefits</strong></td>
<td>Improves survival, QoL, and functional capacity</td>
<td>Improverd QoL and functional capacity</td>
</tr>
<tr>
<td>Limited benefit in severe emphysema</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Risks</strong></td>
<td>Significant morbidity and mortality</td>
<td>Significant morbidity and mortality</td>
</tr>
<tr>
<td>Minimal</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>High risk of mortality</td>
<td>Very few patients qualify</td>
</tr>
<tr>
<td>Limited clinical benefit</td>
<td>~200 procedures/year(^b)</td>
<td>&lt;1000 transplants/year(^c,d)</td>
</tr>
</tbody>
</table>

Bronchoscopic Lung Volume Reduction Represents an Option for Severe Emphysema Patients

Advanced COPD

Emphysema predominant phenotype with severe hyperinflation

- Large bulla: Bullectomy
- No large bulla: Heterogeneous emphysema

Heterogeneous emphysema

- No collateral ventilation: LVRS, Valves, Coils
- + collateral ventilation: LVRS

Homogeneous emphysema

- No collateral ventilation: Valves, Coils, LVRS
- + collateral ventilation: Coils, LVRS

Not candidate for bullectomy, bronchoscopic lung volume reduction, or lung volume reduction surgery

Lung transplant


a At some but not all centers.
Severe Emphysema Represents a Substantial Unmet Need

- Severe emphysema affects an estimated 1.2 million people in the United States\(^a\)
- Lung hyperinflation is strongly associated with patient-centered outcomes: dyspnea, exercise capacity, and daily physical activity\(^b\)
- Reducing hyperinflation improves clinical outcomes and quality of life
- Current treatment options for severe emphysema patients are limited
  - Surgical options (LVRS and lung transplant) are limited by patient eligibility, high procedural risks and complications, and increased morbidity and mortality
  - Current pharmacologic options have limited benefit in severe emphysema patients


**A nonsurgical lung reduction therapy is needed that is effective in reducing hyperinflation in patients with heterogeneous and homogeneous emphysema and severe hyperinflation**