COPD Part III:
LVRS, BiPAP, and Transplantation

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Educational Objectives:
1. Review selection criteria for and outcomes of lung volume reduction surgery (LVRS) and bronchoscopic lung volume reduction (BLVR)
2. Review indications for and outcomes of non-invasive nocturnal ventilation
3. Outline when to consider lung transplantation for COPD

Scenario 1:
Mr. S is a 62-year-old male with severe COPD (FEV1 of 38% predicted). You have been following him for several years and have treated him with fluticasone/salmeterol 250/50 1 puff twice daily, tiotropium 18 mcg 1 capsule inhaled daily, and albuterol 2 puffs or a nebulizer treatment every 6 hours as needed. About a year ago, you prescribed roflumilast 500 mcg oral once daily due to a history of several exacerbations in the preceding year and symptoms of chronic bronchitis. He says he initially had some loss of appetite and lost 6 pounds, but he feels better now and denies ongoing side effects. He thinks it may be helping a little bit, but he still struggles with severe dyspnea despite regular aerobic exercise. A friend told him to ask about lung volume reduction surgery and he wonders if he is a candidate.

Question 1: What patient characteristics are favorable for LVRS? What are the potential risks and benefits?

LVRS involves surgical resection of severely emphysematous lung tissue from one or both upper lung zones. The resection is non-anatomic (i.e. not a lobectomy or segmentectomy). Up to a third of lung tissue may be removed from each lung, and the surgeon will attempt to balance removal of non-functional tissue with preservation of as much functional tissue as possible. Techniques for lung tissue removal include median sternotomy, VATS, and thoracotomy.

- **Mechanism:** There are several postulated mechanisms of benefit:
  - First, as the remaining lung stretches to fill the evacuated space in the chest, elastic recoil is increased, thereby increasing stenting forces holding open small airways and reducing small airways resistance allowing for improved expiratory airflow.
  - Second, the reduction in overall volume of the chest returns the diaphragm toward a more normal upward resting position, restoring some mechanical advantage.
Third, resection of dead space in the lung may improve V/Q matching, leading to better gas exchange despite the decrease in overall surface area.

- **Patient selection:** Indications for LVRS include severe dyspnea despite aggressive treatment with bronchodilators, oxygen as necessary, and exercise training (preferably pulmonary rehabilitation). Table 1 outlines the additional patient characteristics that are favorable and unfavorable for LVRS in detail.

- **Testing:** To determine candidacy for LVRS should include the following:
  - Full pulmonary function tests with plethysmographic lung volumes (gas dilution methods may significantly underestimate volumes)
  - High-resolution chest CT without contrast to assess severity and distribution of emphysema
  - Arterial blood gas to exclude significant hypercapnia
  - Transthoracic echocardiogram to exclude significant pulmonary hypertension
  - Quantitative V/Q scan can also be helpful to corroborate apical lung destruction (demonstrated by apical hypoperfusion on posterior projections).
  - Cardiopulmonary exercise testing by cycle ergometry on 30% oxygen is not strictly necessary but can help to distinguish whether a patient may derive a mortality benefit from the procedure.

<table>
<thead>
<tr>
<th>Table 1: Selection criteria for lung volume reduction surgery</th>
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<tbody>
<tr>
<td><strong>Favorable characteristics</strong></td>
</tr>
<tr>
<td>Severe, apical predominant emphysema</td>
</tr>
<tr>
<td>Severe obstruction (FEV₁ ≤45% pred)</td>
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<tr>
<td>Severe air trapping (ideally RV &gt;200% pred, TLC &gt;100%)</td>
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<tr>
<td>Apical hypoperfusion on V/Q (&lt;10% perfusion to upper lung thirds)</td>
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<tr>
<td>Apical air trapping on V/Q (long tracer half life in upper lung thirds)</td>
</tr>
<tr>
<td>Low exercise capacity after completion of pulmonary rehab (&lt;25 W on cycle ergometry for women, &lt;40 for men)</td>
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<td>Single organ disease</td>
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*Higher risk of early mortality (<90 days post-procedure) based on the NETT Trial (see below).

**National Emphysema Treatment Trial (NETT) (NEJM 2003)**

**Study design:** Unblinded randomized control trial randomizing 1218 subjects with severe COPD to LVRS or continued maximal medical management. Baseline assessments and eligibility were determined after completing pulmonary rehab to exclude the effect of exercise conditioning.

**Inclusion criteria:**
- **Confirmed diagnosis of COPD with**
  - CT scan evidence of bilateral emphysema
  - FEV₁ ≤45% predicted and bilateral emphysema
  - TLC ≥100% predicted & RV ≥150% predicted
  - PₐCO₂ ≤60 mmHg & PₐO₂ ≥45 mmHg
  - BMI ≤31.1 (males) or ≤32.3 (females)
  - Nonsmoker for ≥4 mos.
Exclusion criteria:
- FEV1 ≤20% predicted and either homogeneous disease or DLCO ≤20% predicted (criterion added at interim analysis due to increased mortality)
- CT scan evidence of diffuse emphysema judged unsuitable for LVRS
- Inability to perform valid DLCO maneuver (also added at interim)
- Previous sternotomy or lobectomy, giant bulla, LVRS, or pulmonary nodule requiring surgery
- Pulmonary hypertension defined via RHC as PA systolic ≥45 or mean ≥35
- MI within 6 months of baseline
- CHF (EF <45%)
- Uncontrolled HTN (SBP >200, DBP>110)
- Clinically significant bronchiectasis
- Daily use of prednisone >20 mg
- O₂ requirement >6 L/min
- History of recurrent infections with clinically significant daily sputum production
- Six-minute walk distance <140 m after rehab
- Comorbid disease is expected to compromise survival or interfere with the completion of tests, therapy or follow-up over the course of the study

Intervention: LVRS by either VATS or median sternotomy vs. medical management alone.

Primary Outcomes: Survival and maximal exercise capacity.

Results: At an interim analysis, the subgroup with FEV1 ≤20% predicted and either homogeneous disease or DLCO ≤20% predicted was found to have significantly higher mortality with LVRS and were subsequently excluded from the trial.

Overall mortality was not different between treatment groups, even after excluding these high-risk subjects. The LVRS group had a greater chance of a 10 W improvement in exercise capacity (16% vs. 3%, p<0.001).

Among the subgroup of subjects (at least partially conceived a priori) with predominantly upper lobe emphysema and a lower exercise capacity (max workload <25 W for women, <40 W for men), mortality was lower in the LVRS group (risk ratio for death 0.47, p=0.005). In contrast, those with non-upper lobe predominant emphysema and a higher exercise capacity had a higher mortality with LVRS (risk ratio for death 2.06, p=0.02).

Adverse events: Overall mortality 5% in LVRS group. Other adverse events included re-intubation (22%), air-leak >7 days (~40%), arrhythmias (19%), pneumonia (18%), and failure to wean (trach required in 8%). MI (1%) and stroke (<1%) were rare.
**Figure 1.** Improvement in exercise capacity and health-related quality of life at 24 months. Above and below from the National Emphysema Treatment Trial (NEJM 2003).

### Table: Improvement in Exercise Capacity and Health-Related Quality of Life

<table>
<thead>
<tr>
<th>Patients</th>
<th>Improvement in Exercise Capacity</th>
<th>Improvement in Health-Related Quality of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery Group</td>
<td>Medical-Therapy Group</td>
</tr>
<tr>
<td>All patients</td>
<td>54/371 (15)</td>
<td>10/378 (3)</td>
</tr>
<tr>
<td>High-risk†</td>
<td>4/58 (7)</td>
<td>1/48 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>50/313 (16)</td>
<td>9/330 (3)</td>
</tr>
</tbody>
</table>

**Subgroups‡:**

1. **Predominantly upper-lobe emphysema**
   - Low exercise capacity: 25/84 (30) 0/92 — <0.001
   - High exercise capacity: 17/115 (15) 4/138 (3) 5.81 0.001
2. **Predominantly non-upper-lobe emphysema**
   - Low exercise capacity: 6/49 (12) 3/41 (7) 1.77 0.50
   - High exercise capacity: 2/65 (3) 2/59 (3) 0.90 1.00

**Figure 2.** Kaplan-Meier estimates of the probability of death as a function of the number of months after randomization. High-risk patients were defined as having an FEV1 <20% predicted and either homogenous emphysema or a DLCO <20% predicted from National Emphysema Treatment Trial (NEJM 2003).

- **A** All Patients (N=1218)
- **B** High-Risk Patients (N=140)
- **C** Non-High-Risk Patients (N=1078)
- **D** Upper-Lobe Predominance, Low Base-Line Exercise Capacity (N=290)
- **E** Upper-Lobe Predominance, High Base-Line Exercise Capacity (N=419)
- **F** Non-Upper-Lobe Predominance, Low Base-Line Exercise Capacity (N=149)
- **G** Non-Upper-Lobe Predominance, High Base-Line Exercise Capacity (N=220)
Summary: Surgical LVRS can help with the removal of lung tissue in severe emphysema to enable improvement of physiologic status; leading to improved exercise tolerance and reduced mortality. There was an early risk of death in the first three months for those who underwent LVRS, however, long-term outcomes (>36 months) show a benefit of surgery over medical therapy for appropriately chosen candidates in terms of improving lung function, quality of life and exercise capacity. Candidates likely to garner the most benefit from LVRS are those with apical predominant emphysema and low exercise capacity. Interestingly, although early mortality (<90 d) was increased in the entire homogeneous or basilar predominant group after exclusion of the high risk (FEV1 ≤20% predicted and either homogeneous disease or DLCO ≤20% predicted) phenotype, those with homogeneous disease and a low exercise capacity ultimately did not have higher long-term mortality compared with medical therapy (the survival curves crossed, indicating early mortality in the surgery group followed by a late survival benefit, such that the overall difference was statistically insignificant, with the surgery group technically having the numerically lower mortality). In fact, Medicare approved the procedure for the homogeneous low-exercise group, although not all centers recommend LVRS for this group.

Question 2: What other options for lung volume reduction might be considered for Mr. S?

Bronchoscopic lung volume reduction (BLVR) has been demonstrated to be a non-surgical alternative to LVRS for symptomatic patients with heterogenous emphysema and significant hyperinflation. While several methods for achieving BLVR are under investigation, the best studied (and only FDA-approved) method is endobronchial valve placement. This consists of placing one-way valves in the airways leading to areas of hyperinflated and emphysematous lung. These valves allow for expiration of air, but close during inspiration and prevent air from passing into an area of lung resulting in collapse of the distal lobe, thereby improving hyperinflation. As mentioned in the previous section for LVRS, dyspnea decreases due to improved diaphragm and chest wall mechanics, improved recoil, and in some cases re-expansion of less affected regions of lung.

Question 3: What factors must be weighed when considering BLVR?

BLVR carries a high risk of pneumothorax. As the target lobe collapses, the ipsilateral untreated lobe expands and stretches. As this part of the lung is also typically affected with some degree of emphysema, lung defects (blebs, bullae, etc.) may rupture during rapid expansion. This can result in pneumothorax, a complication of up to 34% of BLVR procedures. A number of factors associated with pneumothorax and poor outcomes following valve placement are listed in the table below (van Dijk M et al. 2021). Consequently, appropriate patient selection is very important (Fernandez-Bussy et al. 2018, Herth F. et al. 2017). Mortality following valve placement is approximately 3%.

Scenario 1 (cont.):
On evaluation, Mr. S has an FEV1 of 38% predicted, TLC 110% predicted, RV 145% predicted, and DLCO 32% predicted. His CT shows severe, relatively homogeneous emphysema. His ABG on room air is 7.32/65/54. Echocardiogram shows normal size and function for both his LV and RV with an estimated PASP of 44 mmHg. You explain that he is not a candidate for LVRS due to homogeneous emphysema, insufficient air-trapping, and significant hypercapnia.
**Table 2: Selection criteria for bronchoscopic lung volume reduction**

<table>
<thead>
<tr>
<th>Favorable characteristics</th>
<th>Unfavorable characteristics</th>
</tr>
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<tbody>
<tr>
<td>• Severe, heterogenous emphysema</td>
<td>• Insufficient obstruction (FEV₁ ≤45% pred)</td>
</tr>
<tr>
<td>• Severe obstruction (FEV₁ ≤45% pred)</td>
<td>• Insufficient residual FEV₁ (&lt;15% pred)</td>
</tr>
<tr>
<td>• Severe air trapping (RV &gt;175% pred)</td>
<td>• Insufficient air trapping (RV &lt;175% pred)</td>
</tr>
<tr>
<td>• Resting hyperinflation (TLC &gt;100% pred)</td>
<td>• Insufficient diffusion (DLCO &lt;20% pred)</td>
</tr>
<tr>
<td>• 6MWD of less than 500 m</td>
<td>• Significant cardiac disease (Reduced EF, recent MI, persistent bradycardia, etc)</td>
</tr>
<tr>
<td>• BMI &lt; 33</td>
<td>• pCO₂ ≥50</td>
</tr>
<tr>
<td>• No tobacco uses in last 4 months</td>
<td>• PASP &gt;45 (or mean PA &gt;35)</td>
</tr>
<tr>
<td>• No evidence of collateral lobar ventilation (Chartis® negative)</td>
<td>• 6MWD of less than 100m</td>
</tr>
<tr>
<td>• Completed pulmonary rehab program within 6 months</td>
<td>• Giant bullae involving &gt;30% of either lung</td>
</tr>
<tr>
<td>• mMRC of at least 2</td>
<td>• Daily prednisone of 20mg or more</td>
</tr>
<tr>
<td>• On maximal inhaler therapy</td>
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Evaluating for the presence of collateral ventilation is an essential component of a BLVR evaluation. Airflow from adjacent lobe(s) prevents collapse of the target lobe. This results in a significant number of patients unable to undergo BLVR. Fissure completeness is used to determine the likelihood of collateral ventilation and it should be ≥ 80% for endobronchial valves to be successful (Fernandez-Bussy et al. 2018).

Fissure completeness can be assessed using computer software (StratX and SeleCT) that is proprietary for each type of valve. Fissure integrity can also be assessed in the operating room prior to valve placement by occluding the target lobe and measuring whether or not collateral ventilation is present. In addition to measuring fissure completeness, the software utilizes CT densitometry to estimate lobar emphysema involvement. A higher percentage of < -910 Hounsfield units (HU) indicates more extensive emphysematous destruction. An example of a StratX® report is shown below in Figure 3.
Question 4: What are outcomes for BLVR procedures?

For suitable patients, outcomes after BLVR are favorable. Four major randomized controlled trials have studied endobronchial valves using two different proprietary valve systems, Zephyr® and Spiration®. The LIBERATE and REACH trials evaluated the Zephyr® valve and the EMPROVE and TRANSFORM trials evaluated the Spiration® valve, each comparing valve placement to standard of care COPD management. These studies have consistently demonstrated improvement in lung function, exercise, and quality of life for patients who received BLVR. Figure 4 shows outcomes from the LIBERATE trial. There is inadequate evidence for BLVR with regard to mortality, however. Some have reported observations of survival benefit in those who experience lobar atelectasis following intervention compared to those who do not (Gompelmann D et al. 2019). The most common adverse event of valve placement is pneumothorax as mentioned above. Valve placement can also be complicated by exacerbations.
Question 5: Would Mr. S benefit from non-invasive positive pressure ventilation at night?

Non-invasive positive pressure ventilation (NIPPV, e.g. BiPAP) is an established, proven therapy for severe acute exacerbations of COPD, reducing mortality and subsequent need for intubation and mechanical ventilation. Similarly, the data for NIPPV in patients with an overlap of COPD and sleep disordered breathing show consistent benefit (Marin et al. 2010). While several early trials of nocturnal NIPPV in patients with stable COPD failed to show benefit (Casanova et al. 2000, Clini et al. 2002), more recent trials utilizing higher inspiratory pressures have shown benefit.

A meta-analysis (JAMA, 2020) of 15 RCTs and 6 observational studies has recently shown significant support for the use of home NIPPV in COPD patients. A review of BiPAP compared to no device showed a lower risk of mortality (OR 0.66 (96% CI:0.51-0.87), p=0.003), as well as a reduction in all-cause hospital admissions and a reduced need for intubation. Of note, there was no significant improvement found in quality of life.

Figure 4. Summary of responders based on minimal clinically important difference for variables assessed in the LIBERATE study of Zephyr EBV (AJRCCM 2018).
ATS Guidelines (Macrea et al. 2020) support the above findings with their recommendations that nocturnal NIPPV can be considered in patients with chronic stable hypercapnia. Prior to initiation of NIPPV, patients should be screened for OSA and undergo a sleep study if there is concern given the well-established benefit of treating OSA in COPD. If a patient screens low risk for OSA, then NIPPV can be initiated. It is critical to point out that studies demonstrating benefit of NIPPV in stable hypercapnic COPD utilized very high IPAP, in excess of 20 cmH2O. Earlier studies that failed to show benefit employed lower pressures. Given the inherent difficulty tolerating high inspiratory pressures, NIPPV can be initiated at lower pressures and titrated up as tolerated to achieve the goal of normalizing PCO2 levels per ATS guidelines.

ATS guidelines recommend NOT initiating NIPPV during an admission for acute on chronic hypercapnic respiratory failure and reassessing 2-4 weeks after discharge. In very rare circumstances, carefully selected hospitalized patients might be appropriate for NIPPV initiation, particularly those with a high risk of readmission or known chronic hypercapnia between hospitalizations.

To qualify a stable COPD patient for home NIPPV, insurance criteria (Medicare guidelines) generally require that the patient have symptoms (such as fatigue, dyspnea, morning headaches, etc.) and any one of the following physiologic criteria:

- **chronic hypercapnia** (arterial pCO2 ≥52)
- PaCO2 of 50 to 54 mm Hg and hospitalization related to recurrent (2 in a 12-month period) episodes of hypercapnic respiratory failure
- nocturnal hypoxia (SaO2 ≤88% for ≥5 min out of at least 2 hours of nocturnal recording time on 2 L/min or patients baseline O2 dose, whichever is higher) exclusion of OSA

### Scenario 1 (cont.):

Mr. S undergoes a sleep study, which demonstrates sleep-related hypoventilation with an oxygen saturation nadir of 84% on his chronic supplemental oxygen at 2 L/min. There are no significant obstructive apneas. During the study, he spends 57 minutes with an oxygen saturation of 88% or less. BiPAP is initiated and titrated to settings of 20/5 cmH2O. He feels it helps him rest more comfortably, but over the next 2 years his dyspnea and lung function impairment continue to progress. He asks you if he may be a candidate for lung transplantation.

### Question 6: What factors determine when it is appropriate to refer for lung transplant?

Timing of referral and listing vary among centers but many use ISHLT consensus guidelines to aid in their decision making (see Table 3).
Table 3: Selection Criteria for Referral and Listing for Lung Transplantation in COPD

<table>
<thead>
<tr>
<th>Timing of Referral</th>
<th>Timing of Listing</th>
</tr>
</thead>
<tbody>
<tr>
<td>• BODE score of 5-6 with additional risk factor(s) suggestive of increased mortality:</td>
<td>• BODE score of 7-10</td>
</tr>
<tr>
<td>1. Frequent exacerbations,</td>
<td>• Additional factors which may prompt listing:</td>
</tr>
<tr>
<td>2. Increase in BODE Score of &gt;1 over the past month</td>
<td>1. FEV1 of &lt;20%</td>
</tr>
<tr>
<td>3. Pulmonary artery: aorta diameter &gt;1 on CT scan,</td>
<td>2. Presence of moderate to severe pulmonary hypertension</td>
</tr>
<tr>
<td>4. FEV1 20-25%</td>
<td>3. History of severe exacerbations</td>
</tr>
<tr>
<td>• Clinical deterioration despite maximal medical therapy, pulmonary rehabilitation,</td>
<td>4. Chronic hypercapnia</td>
</tr>
<tr>
<td>oxygen and nocturnal NIPPV (if indicated)</td>
<td></td>
</tr>
<tr>
<td>• Poor quality of life unacceptable to patient</td>
<td></td>
</tr>
<tr>
<td>• For a candidate appropriate for bronchoscopic or surgical LVRS; simultaneous referral to lung transplant is appropriate</td>
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There are many risk factors for a potentially poor lung transplant outcome. These may change over time. Below you will find a brief list of absolute contraindications to transplant (see ISHLT reference above):

- Lack of patient willingness or acceptance of transplant
- Malignancy with high risk of recurrence or death related to cancer
- Glomerular filtration rate <40mL/min/1.73m2 unless being considered for multi-organ transplant
- Acute coronary syndrome or myocardial infarction within 30 days (excluding demand ischemia)
- Stroke within 30 days
- Liver cirrhosis with portal hypertension or synthetic dysfunction unless being considered for multi-organ transplant
- Acute liver failure
- Acute renal failure with rising creatinine or on dialysis and low likelihood of recovery
- Septic shock
- Active extrapulmonary or disseminated infection
- Active tuberculosis infection
- HIV with detectable viral load
- Limited functional status (e.g. non-ambulatory) with poor potential for post-transplant rehabilitation
- Progressive cognitive impairment
- Repeated episodes of non-adherence without evidence of improvement (not applicable for pediatric patients)
- Active substance use or dependence including current tobacco use, vaping, marijuana smoking or IV drug use
- Other severe uncontrolled medical condition expected to limit survival after transplant

Patients with COPD may be listed for either single or bilateral lung transplantation. The presence of significant pulmonary hypertension is a relative contraindication, and severe suppurative airways disease is an absolute contraindication to single lung transplantation. Whether to list a COPD patient for single lung transplantation is somewhat controversial. Post single-lung transplant, native lung hyperinflation (enlargement of bullous emphysema of the native lung) can occur, but this does not appear to affect clinical outcomes.
References:


