# COPD – Advanced Bronchoscopic Management

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# Introduction

- Chronic Obstructive Pulmonary Disease - structural lung abnormalities, impaired lung function, and resultant chronic respiratory symptoms such as dyspnea, cough, and exercise limitation
- Loss of elastic recoil - early airway closure during exhalation, air trapping and hyperinflation
- Diaphragm - flattened, mechanically disadvantaged position precipitating breathlessness and exercise intolerance
- Treatment - long-acting bronchodilators and pulmonary rehabilitation programs decrease hyperinflation but to a limited extent
- Do not address the underlying mechanical disruption and structural damage seen in advanced emphysema

Chest. 2021 May 1;159(5):1833-42

# Advance Bronchoscopic management of COPD

- **Bronchoscopic lung volume reduction**
- Endobronchial valves (Zephyr® endobronchial valve and Spiration Valve System®)
- Endobronchial coils - Lung volume reduction coils (LVRC)
- Thermal Vapor ablation
- Biologic Lung Reduction (hydrogel sealant - AeriSeal® or emphysematous lung sealant (ELS)
- Airway Bypass stents

- **Therapy for Mucus hypersecretion and inflammation**
- Targeted lung denervation
- Bronchial rheoplasty
- Metered Cryospray
- Balloon deobstruction

# A Randomized Trial Comparing Lung-Volume–Reduction Surgery with Medical Therapy for Severe Emphysema

- Multicenter RCT (N=1218)
- 608 to surgery and 610 to medical therapy
- Inclusion criteria
  - Bilateral emphysema on HRCT
  - FEV1 ≤45% predicted
  - TLC ≥100% predicted
  - RV ≥150% predicted
  - Post-pulmonary rehabilitation 6MWD ≥140 m

N Engl J Med 2003;348:2059-73

**Table 2. Mortality among All Patients and in Subgroups.***

| Patients | 90-Day Mortality | | | Total Mortality | | | | |
|---|---|---|---|---|---|---|---|---|
| | Surgery Group | Medical-Therapy Group | P Value | Surgery Group | | Medical-Therapy Group | | Risk Ratio | P Value |
| | *no. of deaths/total no. (% [95% CI])* | | | *no. of deaths/ total no.* | *no. of deaths/ person-yr* | *no. of deaths/ total no.* | *no. of deaths/ person-yr* | | |
| All patients | 48/608 (7.9 [5.9–10.3]) | 8/610 (1.3 [0.6–2.6]) | <0.001 | 157/608 | 0.11 | 160/610 | 0.11 | 1.01 | 0.90 |
| High-risk† | 20/70 (28.6 [18.4–40.6]) | 0/70 (0 [0–5.1]) | <0.001 | 42/70 | 0.33 | 30/70 | 0.18 | 1.82 | 0.06 |
| Other | 28/538 (5.2 [3.5–7.4]) | 8/540 (1.5 [0.6–2.9]) | 0.001 | 115/538 | 0.09 | 130/540 | 0.10 | 0.89 | 0.31 |
| Subgroups‡ | | | | | | | | | |
| Patients with predominantly upper-lobe emphysema | | | | | | | | | |
| Low exercise capacity | 4/139 (2.9 [0.8–7.2]) | 5/151 (3.3 [1.1–7.6]) | 1.00 | 26/139 | 0.07 | 51/151 | 0.15 | 0.47 | 0.005 |
| High exercise capacity | 6/206 (2.9 [1.1–6.2]) | 2/213 (0.9 [0.1–3.4]) | 0.17 | 34/206 | 0.07 | 39/213 | 0.07 | 0.98 | 0.70 |
| Patients with predominantly non–upper-lobe emphysema | | | | | | | | | |
| Low exercise capacity | 7/84 (8.3 [3.4–16.4]) | 0/65 (0 [0–5.5]) | 0.02 | 28/84 | 0.15 | 26/65 | 0.18 | 0.81 | 0.49 |
| High exercise capacity | 11/109 (10.1 [5.1–17.3]) | 1/111 (0.9 [0.02–4.9]) | 0.003 | 27/109 | 0.10 | 14/111 | 0.05 | 2.06 | 0.02 |

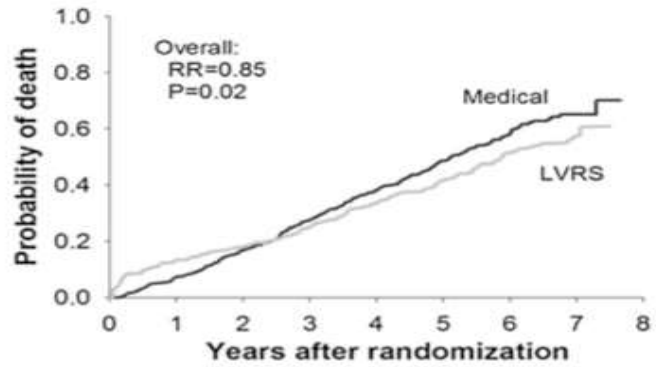
N Engl J Med 2003;348:2059-73

**Table 3. Improvement in Exercise Capacity and Health-Related Quality of Life at 24 Months.***

| Patients | Improvement in Exercise Capacity | | | | Improvement in Health-Related Quality of Life | | | |
|---|---|---|---|---|---|---|---|---|
| | Surgery Group | Medical-Therapy Group | Odds Ratio | P Value | Surgery Group | Medical-Therapy Group | Odds Ratio | P Value |
| | *no./total no. (%)* | | | | *no./total no. (%)* | | | |
| All patients | 54/371 (15) | 10/378 (3) | 6.27 | <0.001 | 121/371 (33) | 34/378 (9) | 4.90 | <0.001 |
| High-risk† | 4/58 (7) | 1/48 (2) | 3.48 | 0.37 | 6/58 (10) | 0/48 | — | 0.03 |
| Other | 50/313 (16) | 9/330 (3) | 6.78 | <0.001 | 115/313 (37) | 34/330 (10) | 5.06 | <0.001 |
| Subgroups‡ | | | | | | | | |
| Predominantly upper-lobe emphysema | | | | | | | | |
| Low exercise capacity | 25/84 (30) | 0/92 | — | <0.001 | 40/84 (48) | 9/92 (10) | 8.38 | <0.001 |
| High exercise capacity | 17/115 (15) | 4/138 (3) | 5.81 | 0.001 | 47/115 (41) | 15/138 (11) | 5.67 | <0.001 |
| Predominantly non–upper-lobe emphysema | | | | | | | | |
| Low exercise capacity | 6/49 (12) | 3/41 (7) | 1.77 | 0.50 | 18/49 (37) | 3/41 (7) | 7.35 | 0.001 |
| High exercise capacity | 2/65 (3) | 2/59 (3) | 0.90 | 1.00 | 10/65 (15) | 7/59 (12) | 1.35 | 0.61 |

N Engl J Med 2003;348:2059-73

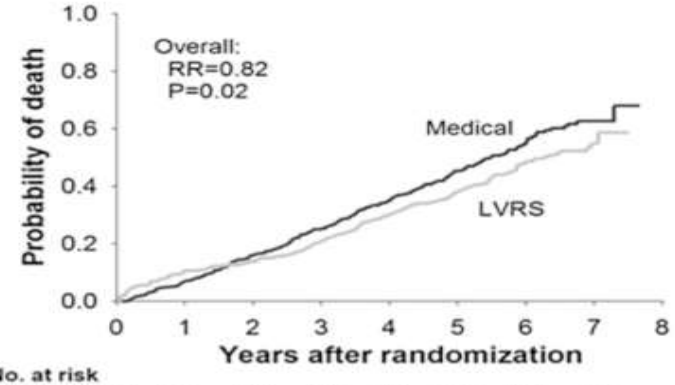
a.




| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| LVRS | 608 | 526 | 496 | 454 | 352 | 227 | 122 | 29 |
| Medical | 610 | 564 | 507 | 441 | 335 | 210 | 99 | 29 |

| Probability of death | | | | | | | |
|---|---|---|---|---|---|---|---|
| LVRS | 0.13 | 0.18 | 0.25 | 0.34 | 0.42 | 0.52 | 0.57 |
| Medical | 0.08 | 0.17 | 0.28 | 0.38 | 0.49 | 0.58 | 0.65 |
| Ratio | 1.79 | 1.09 | 0.91 | 0.89 | 0.86 | 0.89 | 0.88 |
| P | 0.001 | 0.48 | 0.35 | 0.15 | 0.02 | 0.05 | 0.06 |

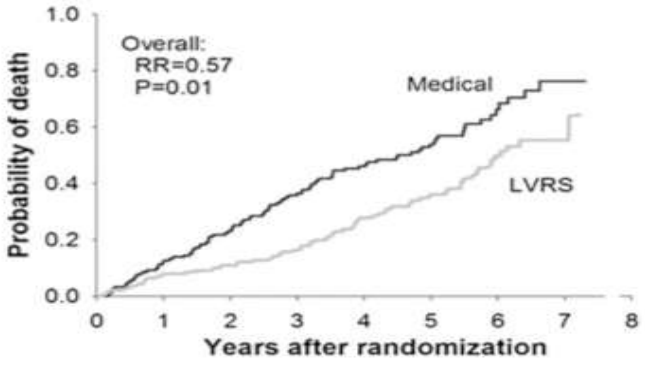
b.




| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| LVRS | 538 | 482 | 460 | 425 | 326 | 207 | 117 | 27 |
| Medical | 540 | 500 | 453 | 403 | 308 | 198 | 94 | 29 |

| Probability of death | | | | | | | |
|---|---|---|---|---|---|---|---|
| LVRS | 0.10 | 0.15 | 0.21 | 0.30 | 0.38 | 0.48 | 0.55 |
| Medical | 0.07 | 0.16 | 0.25 | 0.35 | 0.45 | 0.55 | 0.63 |
| Ratio | 1.40 | 0.90 | 0.83 | 0.86 | 0.85 | 0.88 | 0.88 |
| P | 0.08 | 0.46 | 0.09 | 0.10 | 0.03 | 0.07 | 0.07 |

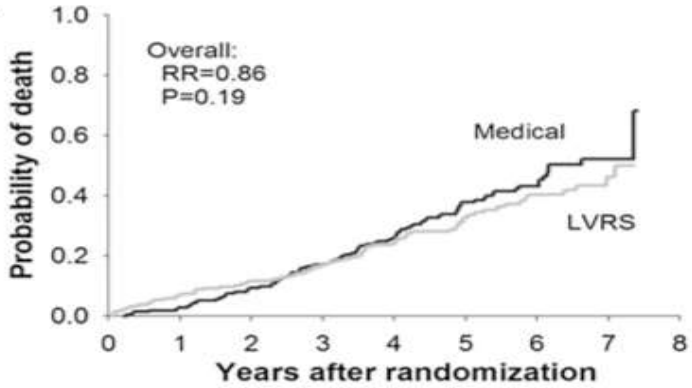
c.




| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| LVRS | 139 | 127 | 123 | 115 | 88 | 57 | 32 | 6 |
| Medical | 151 | 131 | 115 | 95 | 70 | 47 | 16 | 4 |

| Probability of death | | | | | | | |
|---|---|---|---|---|---|---|---|
| LVRS | 0.09 | 0.12 | 0.17 | 0.28 | 0.36 | 0.52 | 0.55 |
| Medical | 0.13 | 0.24 | 0.37 | 0.47 | 0.54 | 0.66 | 0.76 |
| Ratio | 0.65 | 0.48 | 0.47 | 0.59 | 0.67 | 0.78 | 0.72 |
| P | 0.20 | 0.01 | <0.001 | 0.001 | 0.003 | 0.04 | 0.006 |

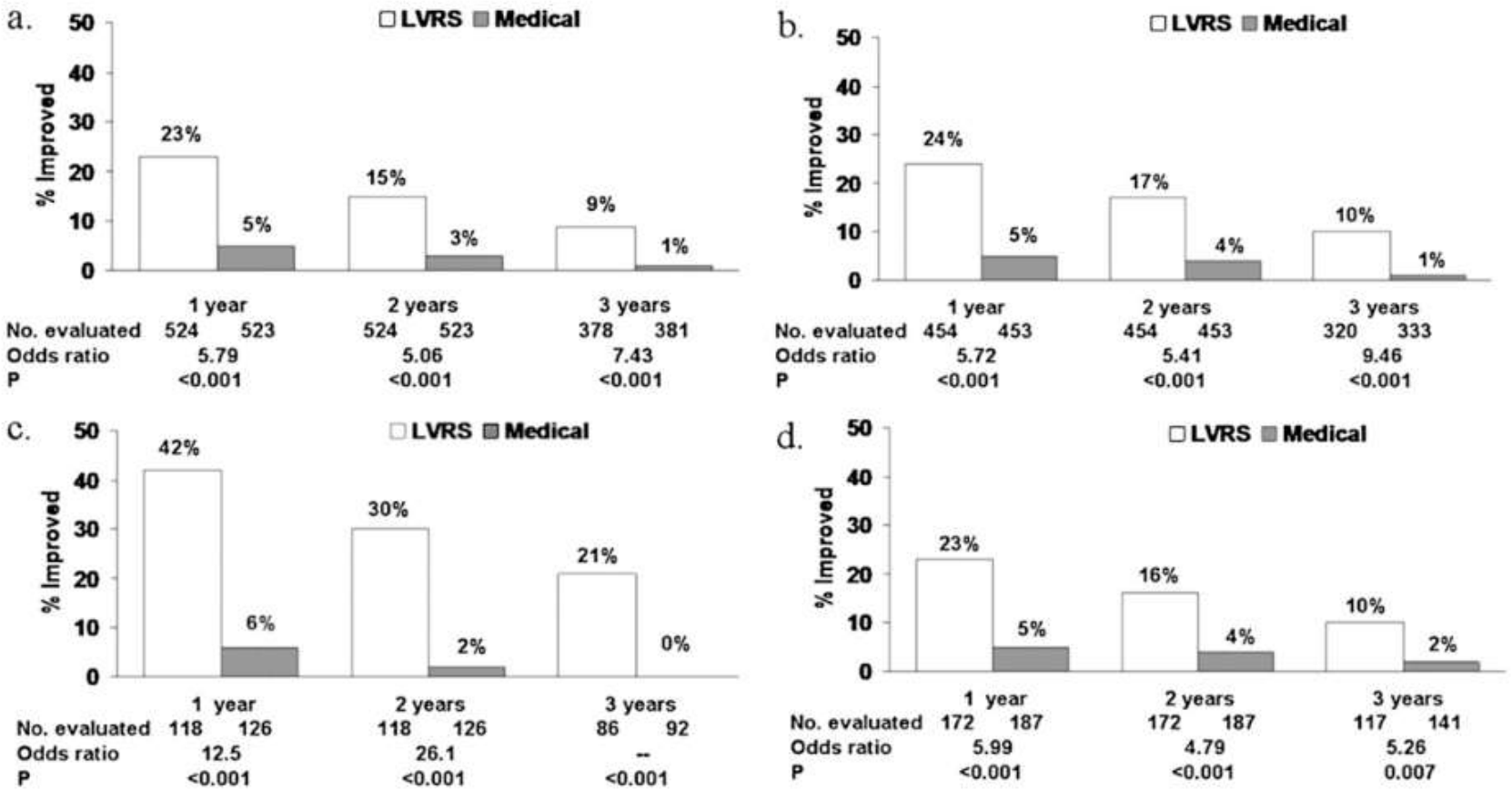
d.




| No.at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| LVRS | 206 | 191 | 181 | 170 | 136 | 80 | 52 | 17 |
| Medical | 213 | 206 | 192 | 176 | 143 | 92 | 55 | 17 |

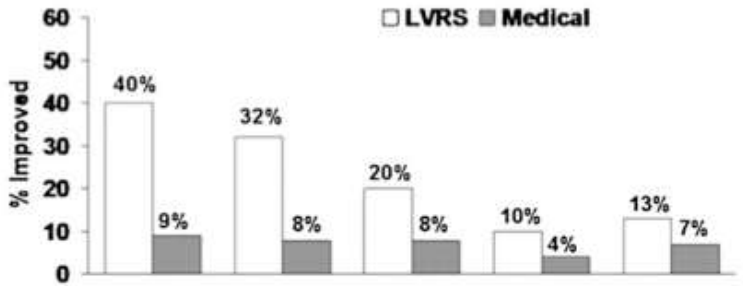
| Probability of death | | | | | | | |
|---|---|---|---|---|---|---|---|
| LVRS | 0.07 | 0.12 | 0.17 | 0.25 | 0.33 | 0.40 | 0.46 |
| Medical | 0.03 | 0.10 | 0.17 | 0.26 | 0.38 | 0.43 | 0.52 |
| Ratio | 2.21 | 1.23 | 1.01 | 0.94 | 0.87 | 0.94 | 0.89 |
| P | 0.07 | 0.46 | 0.98 | 0.71 | 0.32 | 0.61 | 0.39 |

American journal of respiratory and critical care medicine 2011 Oct 15;184(8):881-93



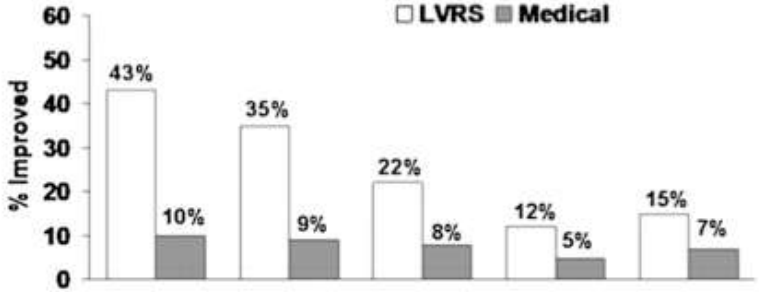

American journal of respiratory and critical care medicine 2011 Oct 15;184(8):881-93

a.



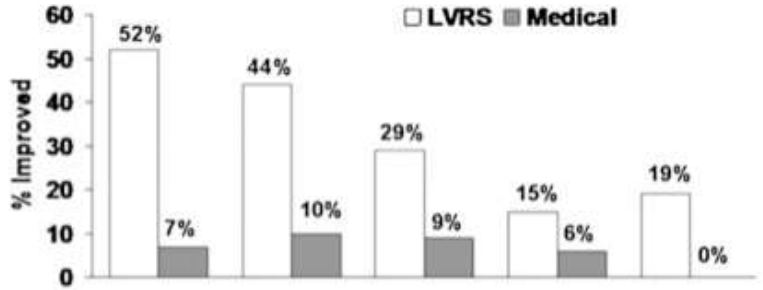

| | 1 year | 2 years | 3 years | 4 years | 5 years |
|---|---|---|---|---|---|
| No. evaluated | 608 610 | 565 568 | 462 466 | 305 305 | 114 122 |
| Odds ratio | 6.50 | 5.27 | 3.06 | 2.63 | 2.16 |
| P | <0.001 | <0.001 | <0.001 | 0.005 | 0.12 |

b.



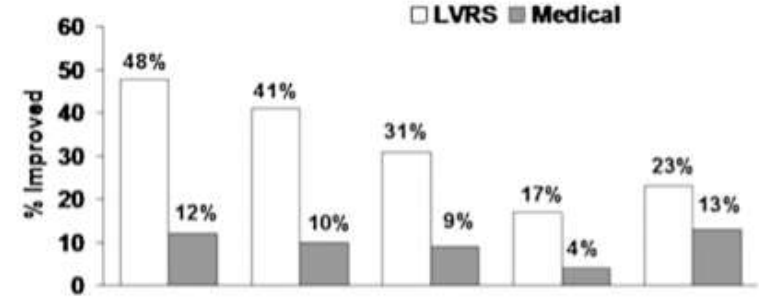

| | 1 year | 2 years | 3 years | 4 years | 5 years |
|---|---|---|---|---|---|
| No. evaluated | 538 540 | 495 498 | 394 407 | 258 270 | 99 112 |
| Odds ratio | 6.72 | 5.33 | 3.26 | 2.80 | 2.32 |
| P | <0.001 | <0.001 | <0.001 | 0.003 | 0.08 |

c.




| | 1 year | 2 years | 3 years | 4 years | 5 years |
|---|---|---|---|---|---|
| No. evaluated | 139 151 | 129 138 | 103 114 | 71 77 | 26 33 |
| Odds ratio | 13.7 | 7.01 | 4.27 | 2.64 | -- |
| P | <0.001 | <0.001 | <0.001 | 0.11 | 0.01 |

d.




| | 1 year | 2 years | 3 years | 4 years | 5 years |
|---|---|---|---|---|---|
| No. evaluated | 206 213 | 190 199 | 143 163 | 95 118 | 43 48 |
| Odds ratio | 6.96 | 6.46 | 4.73 | 4.58 | 2.12 |
| P | <0.001 | <0.001 | <0.001 | 0.003 | 0.27 |

American journal of respiratory and critical care medicine 2011 Oct 15;184(8):881-93

# Bronchoscopic Lung volume reduction

# Inclusion criteria

- Persistence of symptoms despite optimized medical therapy with pulmonary rehabilitation
- Abstinence from smoking
- Modified Medical Research Council (mMRC ≥ 2)
- COPD Assessment Test (CAT score ≥ 10))
- Limitation in exercise performance (6 min walk test (6MWT) distance > 100 m but < 450 m)
- Hyperinflation - total lung capacity (TLC) ≥ 100% predicted and residual volume (RV) ≥ 175% predicted
- Diffusing capacity for carbon monoxide (DLCO) ≥ 20% predicted

1.Chest. 2021 May 1;159(5):1833-42
2.Ajrccm 2018 Nov1;198(9):1151-64
3.Ajrccm2019 Dec 1;200(11):1354-62

# Exclusion criteria

- Severe resting hypoxemia ($PaO_2 < 45$ mm Hg), hypercapnia ($PaCO_2 > 50$ mm Hg), or pulmonary hypertension
- Heart failure (left ventricular ejection fraction < 40%)
- Prior thoracic surgery (previous lobectomy, lung transplantation, or lung volume reduction surgery) in the target lobe
- Frequent infectious exacerbations (chronic bronchitis phenotype or symptomatic bronchiectasis) due to high risk of local microbiologic colonization of endobronchial devices)

1.Chest. 2021 May 1;159(5):1833-42
2.Ajrccm 2018 Nov1;198(9):1151-64
3.Ajrccm2019 Dec 1;200(11):1354-62

- Presence of large bullae, incomplete fissures, significant paraseptal emphysema
- Diffuse Parenchymal lung disease, lung nodules suspicious for malignancy (or those that need to be followed with sequential imaging), and bronchiectasis

1 Chest. 2021 May 1;159(5):1833-42
2.Ajrccm 2018 Nov1;198(9):1151-64
3.Ajrccm Dec 15;196(12):1535-43
4 Journal of Thoracic Imaging. 2021 May 23;36(3):131-41

# Selection of target treatment lobe and collateral ventilation

- Quantitative CT analysis (QCT) to identify target treatment lobes
- QCT - Lobe destruction score based on percentage of low-attenuation areas and fissure completeness score (FCS).
- Most common cut offs for lobe destruction are at least 30% of target lobe > −950 Hounsfield units or at least 50% > −910 Hounsfield units
- Collateral ventilation – Fissure integrity (QCT) and Chartis system

1.N Engl J Med. 2003;348:2059-73
2.Ajrccm 2018 Nov1;198(9):1151-64
3.Ajrccm2019 Dec 1;200(11):1354-62

The % quantitative (<-910HU) emphysema scores were converted to Likert scores using the following conversions:

| % of CT Hounsfield units below -910 (i.e. % of lung suggestive of Emphysema) | Emphysema Score (ES) |
|---|---|
| 1-25% | 1 |
| 26-50% | 2 |
| 51-75% | 3 |
| >75% | 4 |

For the purpose of targeting we defined:
Heterogeneity Score (HS) = Upper Lobe ES - Lower Lobe ES
*(i.e. the absolute value of the difference between the upper and lower emphysema scores)*

*and*

The lung Destruction Score (DS) = Upper lobe ES + Lower lobe ES
*(i.e. the severity of the entire lung per Likert scale ES scoring)*

Targeting then proceeded with the following algorithm:

1. Target the lung with either an Upper or Lower Lobe ES $\geq$ 3 AND an HS score of at least 1
2. If #1 is true for both lungs, target the lung with the highest HS.
3. If #1 is true for both lungs and both lungs have the same HS, target the lung with the highest DS.
4. If both lungs are equally eligible based on points 1-3 above, target the lung with the greater heterogeneity (as calculated using the difference in actual quantitative % emphysema scores determined by the core lab). Within that lung, target the lobe with the greatest quantitative emphysema score.

Fissure integrity was defined as the completeness of the fissure on at least 1 axis (sagittal, axial or coronal views) as classified by the consensus of 2 independent readers at the HRCT core lab.

- Endobronchial valve Placement

# Endobronchial Valves

- Endobronchial valves  - placed in selected target lobe and act as one-way valves allows  allow air to escape during expiration but preclude air from entering during inspiration.
- Lobar atelectasis achieved - lung volume reduction (reduction in residual volume and improvement in diaphragmatic excursion)

Ajrccm 2018 Nov1;198(9):1151-64

# VENT TRIAL(2010)

- Randomized, prospective, multicenter trial
- Endobronchial Valve for Emphysema Palliation Trial (VENT)
- 321 patients enrolled – 220 Endobronchial valve and 101 standard medical therapy
- Primary outcome : Percent change in the FEV1 and distance on the 6-minute walk test in the EBV group compared with the control group, at 6 months after randomization
- Primary safety end point - Difference in the rate of composite of six major complications(Death, empyema, massive hemoptysis, pneumonia distal to valves, pneumothorax or air leak of more than 7 days duration, or ventilator-dependent respiratory failure > 24 hours duration) at 6 months

N Engl J Med 2010;363:1233-44

**Table 2. Primary and Secondary Efficacy Outcomes in the Intention-to-Treat Population (Change from Baseline at 6 Months).***

| Outcome | Endobronchial-Valve Therapy (N=220) | Control (N=101) | Between-Group Difference in Change from Baseline | P Value |
|---|---|---|---|---|
| | *number (95% confidence interval)* | | | |
| **Primary outcome** | | | | |
| $FEV_1$ | | | | |
| Mean absolute percent change from baseline | 4.3 (1.4 to 7.2) | −2.5 (−5.4 to 0.4) | 6.8 (2.1 to 11.5) | 0.005 |
| Mean change in value from baseline — ml | 34.5 (10.8 to 58.3) | −25.4 (−48.3 to −2.6) | 60.0 (21.5 to 98.4) | 0.002 |
| Mean absolute percent change in predicted value from baseline | 1.0 (0.2 to 1.8) | −0.9 (−1.7 to −0.1) | 1.9 (0.5 to 11.2) | 0.007 |
| Distance on 6-min walk test† | | | | |
| Median absolute percent change from baseline | 2.5 (−1.1 to 6.1) | −3.2 (−8.9 to 2.4) | 5.8 (0.5 to 11.2) | 0.04 |
| Median change from baseline — m | 9.3 (−0.5 to 19.1) | −10.7 (−29.6 to 8.1) | 19.1 (1.3 to 36.8) | 0.02 |
| **Secondary outcome** | | | | |
| Mean change in score on SGRQ from baseline‡ | −2.8 (−4.7 to −1.0) | 0.6 (−1.8 to 3.0) | −3.4 (−6.7 to 0.2) | 0.04 |
| Mean change in score on Modified Medical Research Council dyspnea scale from baseline§ | −0.1 (−0.21 to 0.09) | 0.2 (0.01 to 0.37) | −0.3 (−0.50 to −0.01) | 0.04 |
| Mean change in cycle ergometry peak workload from baseline — W | 0.6 (−1.5 to 2.7) | −3.2 (−4.5 to −1.9) | 3.8 (0.1 to 7.5) | 0.05 |
| Median change in supplemental oxygen use from baseline — liters/day† | 0.0 (−117.3 to 117.3) | 0.0 (−148.2 to 148.2) | −12.0 (−76.7 to 52.7) | 0.005 |

N Engl J Med 2010;363:1233-44

**Table 4. Percent Changes in the $FEV_1$ and Distance on the 6-Minute Walk Test at 6 and 12 Months, According to Subgroup of Disease Severity.***

| Subgroup and Outcome | Percent Change from Baseline at 6 Mo | | Percent Change from Baseline at 12 Mo | |
|---|---|---|---|---|
| | Difference between EBV Group and Control Group | P Value† | Difference between EBV Group and Control Group | P Value† |
| | *% (95% CI)* | | *% (95% CI)* | |
| High heterogeneity | | | | |
| $FEV_1$ | 10.7 (3.5 to 17.9) | 0.004 | 13.3 (5.7 to 20.9) | <0.001 |
| Distance on 6-min walk test | 12.4 (4.8 to 20.1) | 0.002 | 7.1 (–0.8 to 14.9) | 0.08 |
| Low heterogeneity | | | | |
| $FEV_1$ | 2.5 (–3.1 to 8.2) | 0.38 | 1.5 (–4.7 to 7.6) | 0.64 |
| Distance on 6-min walk test | –1.0 (–6.4 to 8.4) | 0.80 | –0.6 (–6.4 to 7.7) | 0.84 |
| Complete fissure | | | | |
| $FEV_1$ | 16.2 (8.8 to 23.8) | <0.001 | 17.9 (9.8 to 25.9) | <0.001 |
| Distance on 6-min walk test | 7.7 (–1.8 to 17.2) | 0.14 | 3.9 (–4.0 to 11.8) | 0.31 |
| Incomplete fissure | | | | |
| $FEV_1$ | 2.0 (–3.9 to 7.9) | 0.51 | 2.8 (–3.8 to 9.4) | 0.41 |
| Distance on 6-min walk test | 5.3 (–1.5 to 12.2) | 0.13 | 4.5 (–2.7 to 11.8) | 0.20 |

N Engl J Med 2010;363:1233-44

**Table 3. Major Adverse Events at 90 Days.***

| Event | Endobronchial-Valve Therapy (N=214) | Control (N=87) | P Value† |
|---|---|---|---|
| | *no. (% [95% CI])* | *no. (% [95% CI])* | |
| Patients with any event in the composite of major complications | 9 (4.2 [1.9–7.8]) | 0 (0 [0.0–4.2]) | 0.06 |
| Death‡ | 2 (0.9 [0.1–3.3]) | 0 (0 [0.0–4.2]) | 1.00 |
| Cardiovascular event | | | |
| Arrhythmia | 2 (0.9 [0.1–3.3]) | 0 (0 [0.0–4.2]) | 1.00 |
| Congestive heart failure | 0 (0 [0.0–1.1]) | 1 (1.1 [0.0–6.2]) | 0.29 |
| Coronary artery disease | 2 (0.9 [0.1–3.3]) | 1 (1.1 [0.0–6.2]) | 1.00 |
| Pulmonary or thoracic event | | | |
| COPD exacerbation | | | |
| With hospitalization | 17 (7.9 [4.7–12.4]) | 1 (1.1 [0.0–6.2]) | 0.03 |
| Without hospitalization | 3 (1.4 [0.3–4.0]) | 0 (0 [0.0–4.2]) | 0.56 |
| Pulmonary infection | 4 (1.9 [0.5–4.7]) | 0 (0 [0.0–4.2]) | 0.33 |
| Respiratory failure‡ | 3 (1.4 [0.3–4.0]) | 0 (0 [0.0–4.2]) | 0.56 |
| Pneumonia | | | |
| Not distal to valve | 5 (2.3 [0.8–5.4]) | 2 (2.3 [0.3–8.1]) | 1.00 |
| Distal to valve‡ | 2 (0.9 [0.1–3.3]) | NA | NA |
| New or worsening hypercapnia§ | 2 (0.9 [0.1–3.3]) | 0 (0 [0.0–4.2]) | 1.00 |
| Hypoxemia | 3 (1.4 [0.3–4.0]) | 0 (0 [0.0–4.2]) | 0.56 |
| Hemoptysis | | | |
| Massive‡ | 1 (0.5 [0.0–2.6]) | 0 (0 [0.0–4.2]) | 1.00 |
| Any | 12 (5.6 [2.9–9.6]) | 0 (0 [0.0–4.2]) | 0.02 |
| Pneumothorax or air leak | | | |
| Duration of >7 days‡ | 3 (1.4 [0.3–4.0]) | 0 (0 [0.0–4.2]) | 0.56 |
| Expanding | 3 (1.4 [0.3–4.0]) | 0 (0 [0.0–4.2]) | 0.56 |
| Stable | 3 (1.4 [0.3–4.0]) | 0 (0 [0.0–4.2]) | 0.56 |
| Empyema‡ | 0 (0 [0.0–1.7]) | 0 (0 [0.0–4.2]) | NA |
| Noncardiac chest pain | 1 (0.5 [0.0–2.6]) | 0 (0 [0.0–4.2]) | 1.00 |
| Implant-related event | | | |
| Valve expectoration, aspiration, or migration | 10 (4.7 [2.3–8.4]) | NA | NA |
| Formation of bronchial granulation tissue | 5 (2.3 [0.8–5.4]) | NA | NA |
| Bronchial trauma | 1 (0.5 [0.0–2.6]) | NA | NA |

N Engl J Med 2010;363:1233-44

# Liberate(2018)

- Multicentre randomized controlled trial
- Enrolled patients between oct 2013 and sept 2016
- 190 subjects randomized - 128 in endobronchial valve group and 62 Standard of care group
- Primary outcome - at 1 yr 47.7% EBV and 16.8% subjects in standard of care had a FEV1greater than or equal to 15% (P<0.001)
- Secondary outcomes included difference between EBV and Standard of care groups - absolute change at 1 year in FEV1, St. George's Respiratory Questionnaire (SGRQ), and 6MWD

American journal of respiratory and critical care medicine 2018 Nov 1;198(9):1151-64

# Liberate(2018)

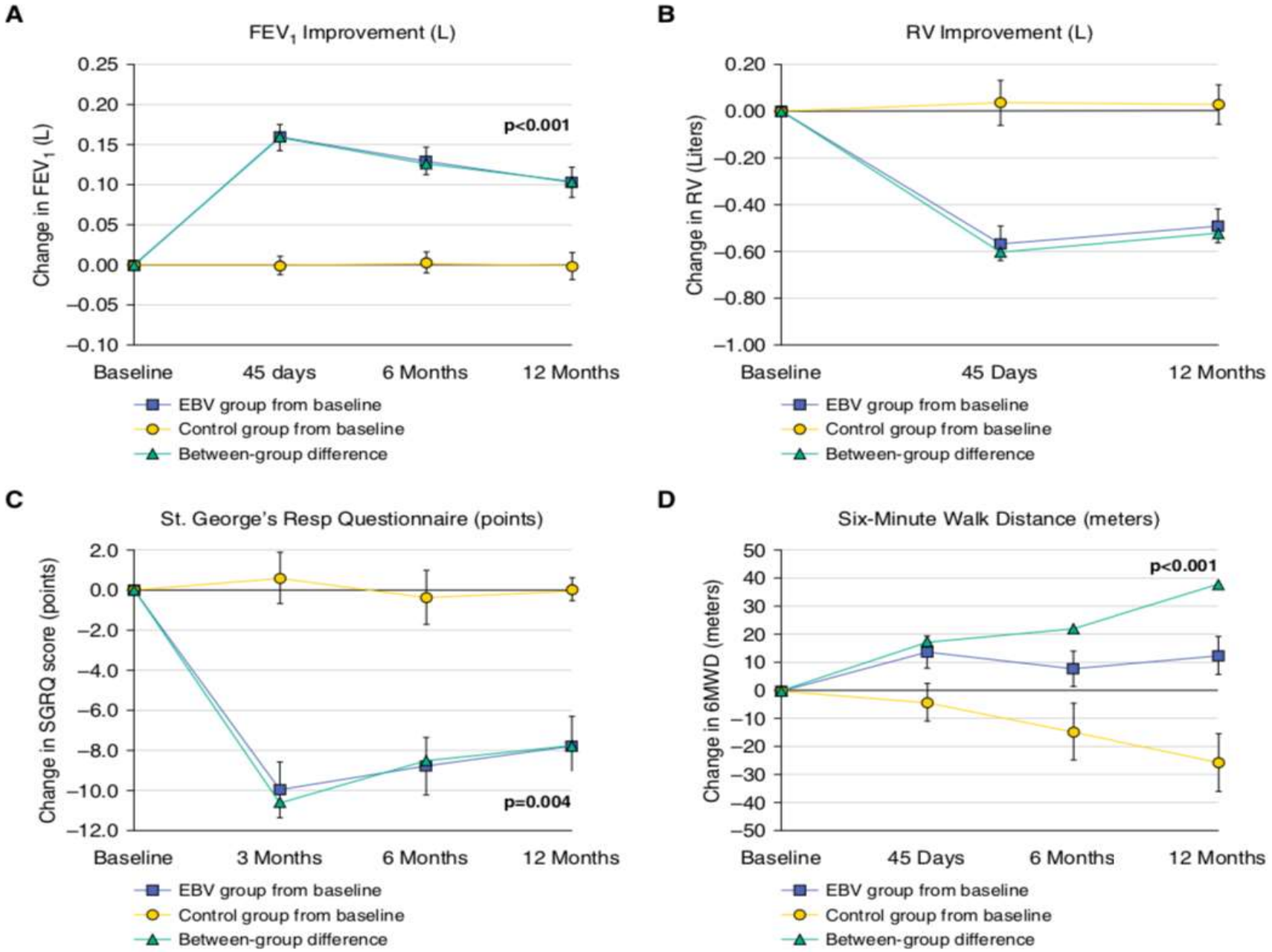
- Intervention : Median of four valves (range, 2–8) placed per 128 EBV subjects either under general anaesthesia 83 (64.8%) or conscious sedation 45 (35.2%)

| Treated lobe | Endobronchial valve group |
|---|---|
| Left upper lobe | 85(66.4%) |
| Left lower lobe | 15 (11.7%) |
| Right upper lobe | 14(10.9%) |
| Right lower lobe | 6(4.9%) |

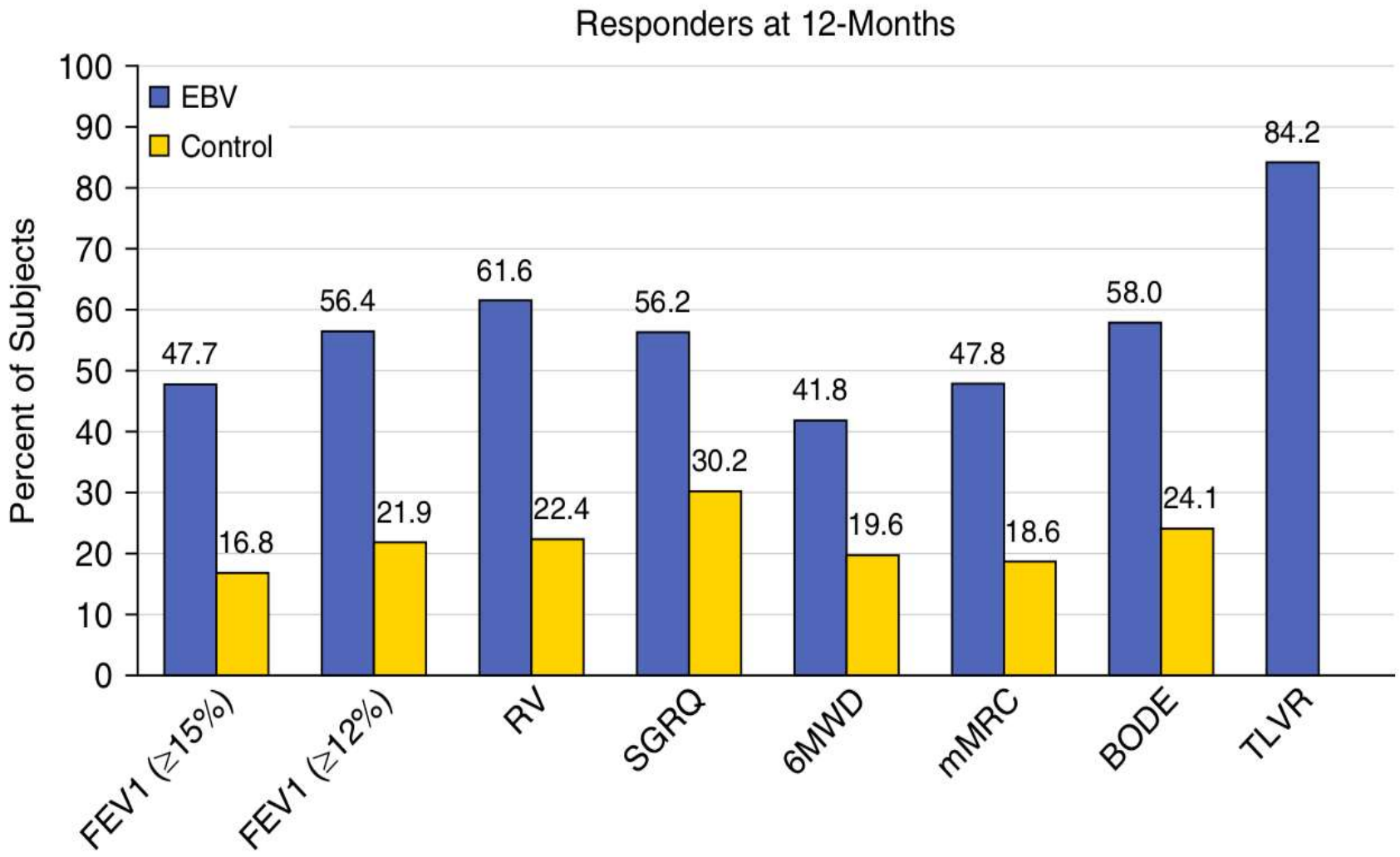
American journal of respiratory and critical care medicine 2018 Nov 1;198(9):1151-64

| Outcome | EBV (*n* = 128) | SoC (*n* = 62) | Between-Group Difference EBV – SoC (95% CI) | *P* Value |
|---|---|---|---|---|
| Primary endpoint[†] | | | | |
| Percent of subjects with post-BD $FEV_1$ (L) improvement of ⩾15% | 47.7 | 16.8 | 31.0 (18.0 to 43.9) | <0.001 |
| Secondary endpoints[‡] (change from baseline to 12 mo) | | | | |
| Post-BD $FEV_1$[‡] | | | | |
| Volume, L | 0.104 ± 0.200 | −0.003 ± 0.194 | 0.106 (0.047 to 0.165) | <0.001 |
| Percent change, % | 17.16 ± 27.93 | −0.80 ± 26.94 | 17.96 (9.84 to 26.09) | <0.001 |
| 6MWD, m | 12.98 ± 81.54 | −26.33 ± 81.50 | 39.31 (14.64 to 63.98) | 0.002[‡] |
| SGRQ score, points | −7.55 ± 15.71 | −0.50 ± 15.50 | −7.05 (−11.84 to −2.27) | 0.004[‡] |
| TLVR | | | | |
| Volume, L | −1.142 ± 0.702 | NA | | |
| Percent change, % | 63.8 ± 36.16 | NA | | |
| Additional endpoints (change from baseline to 12 mo)[§] | | | | |
| $FEV_1$, % predicted[‖] | 4.0 ± 7.84 (128) | −0.3 ± 4.41 (62) | 4.2 (2.1 to 6.4) | <0.001 |
| RV, L | −0.49 ± 0.83 (112) | 0.03 ± 0.66 (58) | −0.522 (−0.77 to −0.27) | <0.001 |
| FRC, L | −0.412 ± 0.768 (112) | 0.014 ± 0.509 (58) | −0.425 (−0.65 to −0.20) | <0.001 |
| TLC, L | −0.319 ± 0.621 (112) | −0.031 ± 0.467 (58) | −0.288 (−0.47 to −0.11) | 0.002 |
| RV/TLC | −0.045 ± 0.079 (112) | 0.005 ± 0.059 (58) | −0.050 (−0.07 to −0.03) | <0.001 |
| IC/TLC | 0.03 ± 0.07 (112) | −0.004 ± 0.04 (58) | 0.03 (0.02 to 0.05) | <0.001 |
| $D_{LCO}$, ml CO/min/mm Hg | 0.559 ± 2.410 (112) | −0.310 ± 1.533 (57) | 0.870 (0.18 to 1.56) | 0.013 |
| $D_{LCO}$, % predicted | 1.80 ± 8.44 (112) | −1.01 ± 6.39 (57) | 2.82 (0.31 to 5.33) | 0.014 |
| mMRC, points | −0.5 ± 1.17 (113) | 0.3 ± 1.03 (59) | −0.8 (−1.1 to −0.4) | <0.001 |
| BODE index, points | −0.6 ± 1.76 (112) | 0.6 ± 1.51 (58) | −1.2 (−1.8 to −0.7) | <0.001 |

American journal of respiratory and critical care medicine 2018 Nov 1;198(9):1151-64




American journal of respiratory and critical care medicine 2018 Nov 1;198(9):1151-64




American journal of respiratory and critical care medicine 2018 Nov 1;198(9):1151-64

# Adverse events

- Post procedure – initial 45 days follow up – 34 patients developed  pneumothorax and 10 patients COPD exacerbation in EBV group
- Post 45 days to 1 yr – 28 patient in EBV group developed COPD exacerbation

American journal of respiratory and critical care medicine 2018 Nov 1;198(9):1151-64

# Improving Lung Function in Severe Heterogenous Emphysema with the Spiration Valve System (EMPROVE) - 2019

- Multicenter, open-label, randomized, controlled trial
- 172 participants  randomized (2:1 randomisation) to treatment (n = 113) or control (n = 59)
- Intervention -  Spiration Valve System  placed to occlude all segments (i.e., lobar, segmental, and/or subsegmental airways)
- The primary outcome -  mean change in post BD  FEV1 from baseline to 6 months between treatment and control groups

American journal of respiratory and critical care medicine. 2019 Dec 1;200(11):1354-62

# Endobronchial Valve Therapy in Patients with Homogeneous Emphysema
# Results from the IMPACT Study

**Table 2.** Absolute Change in Key Parameters from Baseline to 3 Months

| Variable | EBV Group (*n*) | SoC Group (*n*) | ΔEBV − SoC [*Mean (95% CI)*] | *P* Value |
|---|---|---|---|---|
| $FEV_1$, L | 0.10 ± 0.18 (43) | −0.02 ± 0.10 (50) | 0.12 (0.06 to 0.18) | <0.0001 |
| Residual volume, L | −0.42 ± 0.90 (43) | 0.05 ± 0.87 (50) | −0.48 (−0.84 to −0.11) | 0.0113* |
| 6MWD, m | 22.6 ± 66.6 (40) | −17.3 ± 52.8 (50) | 40.0 (15.0 to 65.0) | 0.002* |
| SGRQ total score, points | −8.63 ± 11.2 (37) | 1.01 ± 9.3 (48) | −9.64 (−14.09 to −5.20) | <0.0001* |
| mMRC grade, points | −0.39 ± 1.00 (41) | 0.18 ± 0.98 (50) | −0.57 (−0.98 to −0.16) | 0.007* |
| CAT total score, points | −1.5 ± 5.6 (41) | −0.7 ± 3.7 (49) | −0.9 (−2.9 to 1.1) | 0.374* |
| BODE index score | −0.7 ± 1.5 (39) | 0.4 ± 1.1 (50) | −1.16 (−1.7 to −0.6) | <0.0001† |

Am J Respir Crit Care Med Vol 194, Iss 9, pp 1073–1082, Nov 1, 2016

# Endobronchial Valve Therapy in Patients with Homogeneous Emphysema
# Results from the IMPACT Study

**Table 3.** Responders with Minimal Clinically Important Difference in Key Outcome Measures in Intention-to-Treat Population

| Variable | EBV Group | SoC Group | *P* Value* |
|---|---|---|---|
| $FEV_1$ (L),† MCID ⩾ +15% | 15/43 (34.9%) | 2/50 (4.0%) | 0.0001 |
| $FEV_1$ (L),† MCID ⩾ +12% | 17/43 (39.5%) | 4/50 (8.0%) | 0.0003 |
| $FEV_1$ (L), MCID ⩾ 100 ml | 16/43 (37.2%) | 5/50 (10.0%) | 0.002 |
| RV (ml), MCID ⩽ −430 ml | 19/43 (44.2%) | 9/50 (18.0%) | 0.006 |
| SGRQ, MCID ⩽ −4 points | 21/37 (56.8%) | 12/48 (25.0%) | 0.003 |
| SGRQ, MCID ⩽ −8 points | 17/37 (45.9%) | 4/48 (8.3%) | <0.0001 |
| 6MWD, MCID ⩾ +26 m | 20/40 (50.0%) | 7/50 (14.0%) | 0.0002 |
| mMRC, MCID ⩽ −1 point | 17/41 (41.5%) | 7/50 (14.0%) | 0.003 |

Am J Respir Crit Care Med Vol 194, Iss 9, pp 1073–1082, Nov 1, 2016

# Improving Lung Function in Severe Heterogenous Emphysema with the Spiration Valve System (EMPROVE) - 2019

- At 6 months  treatment group -  0.099 L on average from baseline (95% BCI, 0.069–0.128) and  control group changed by -0 .002 L (95% BCI, -0.030 to 0.026), for a between-group difference of 0.101 L (95% BCI, 0.060–0.141)
- At 12 months, the treatment group improved by 0.067 L on average (95% BCI, 0.031 to 0.103), whereas the control group decreased by -0.032 L (95% BCI, 20.069 to 0.005), for a between-group difference of 0.099 L (95% BCI, 0.048–0.151)

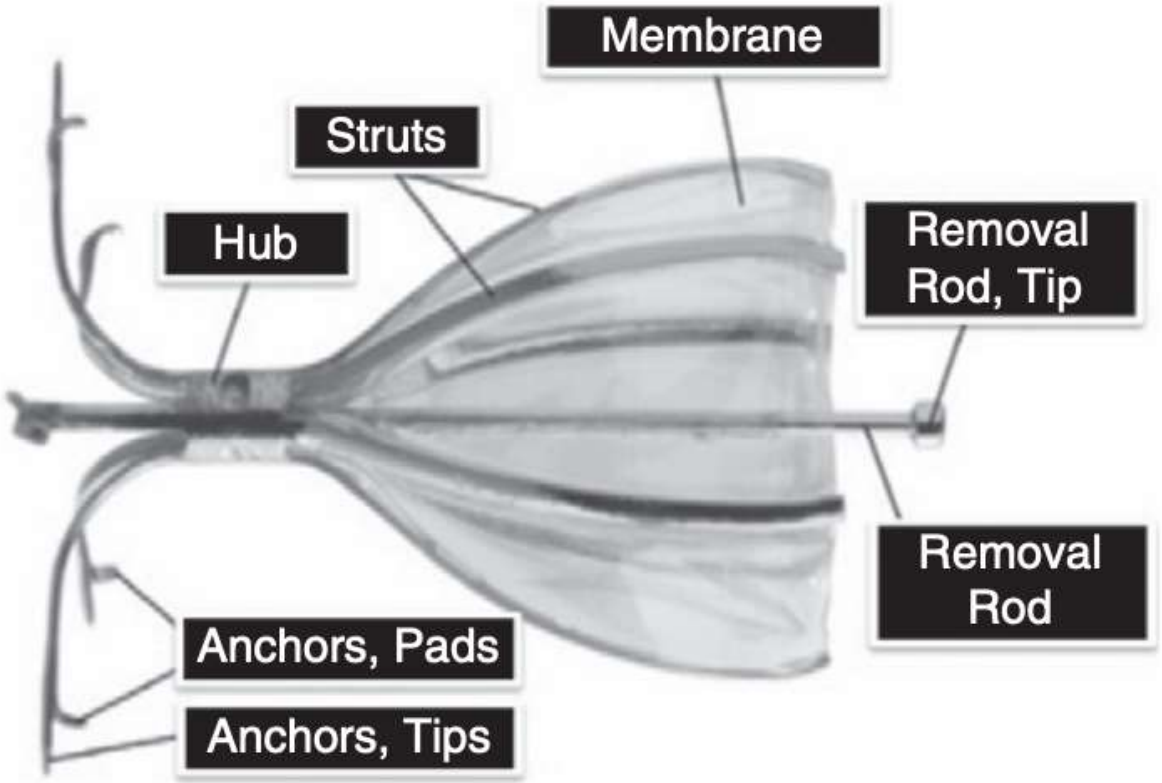
American journal of respiratory and critical care medicine. 2019 Dec 1;200(11):1354-62

# Improving Lung Function in Severe Heterogenous Emphysema with the Spiration Valve System (EMPROVE) - 2019

| Outcome Measure Described as Change from Baseline | Treatment Group [*Mean ± SD (N)*] | Control Group [*Mean ± SD (N)*] | Difference between Groups (*95% BCI*) | Posterior Probability of Superiority |
|---|---|---|---|---|
| TLV, L | | | | |
| 6 mo | −0.974 ± 0.74 (102) | NA | −0.974 (−1.12 to −0.83)* | 1.0000 |
| RV, L | | | | |
| 6 mo | −0.402 ± 0.85 (105) | −0.042 ± 0.58 (50) | −0.361 (−0.59 to −0.13) | 0.9990 |
| RV/TLC | | | | |
| 6 mo | −0.035 ± 0.08 (105) | 0.005 ± 0.04 (50) | −0.039 (−0.06 to −0.02) | 1.0000 |
| SGRQ | | | | |
| 6 mo | −8.1 ± 17.1 (105) | 4.8 ± 10.6 (50) | −13.0 (−17.4 to −8.5) | 1.0000 |
| 12 mo | −5.8 ± 16.8 (95) | 3.7 ± 10.9 (41) | −9.5 (−14.4 to −4.7) | 1.0000 |
| mMRC | | | | |
| 6 mo | −0.6 ± 1.0 (107) | −0.0 ± 0.6 (50) | −0.6 (−0.9 to −0.3) | 1.0000 |
| 12 mo | −0.6 ± 1.1 (94) | 0.2 ± 0.6 (41) | −0.9 (−1.2 to −0.6) | 1.0000 |
| 6MWT, m | | | | |
| 6 mo | −4.4 ± 76.7 (102) | −11.3 ± 51.4 (48) | 6.9 (−14.2 to 28.2) | 0.7438 |

American journal of respiratory and critical care medicine. 2019 Dec 1;200(11):1354-62

# Spiration Valve



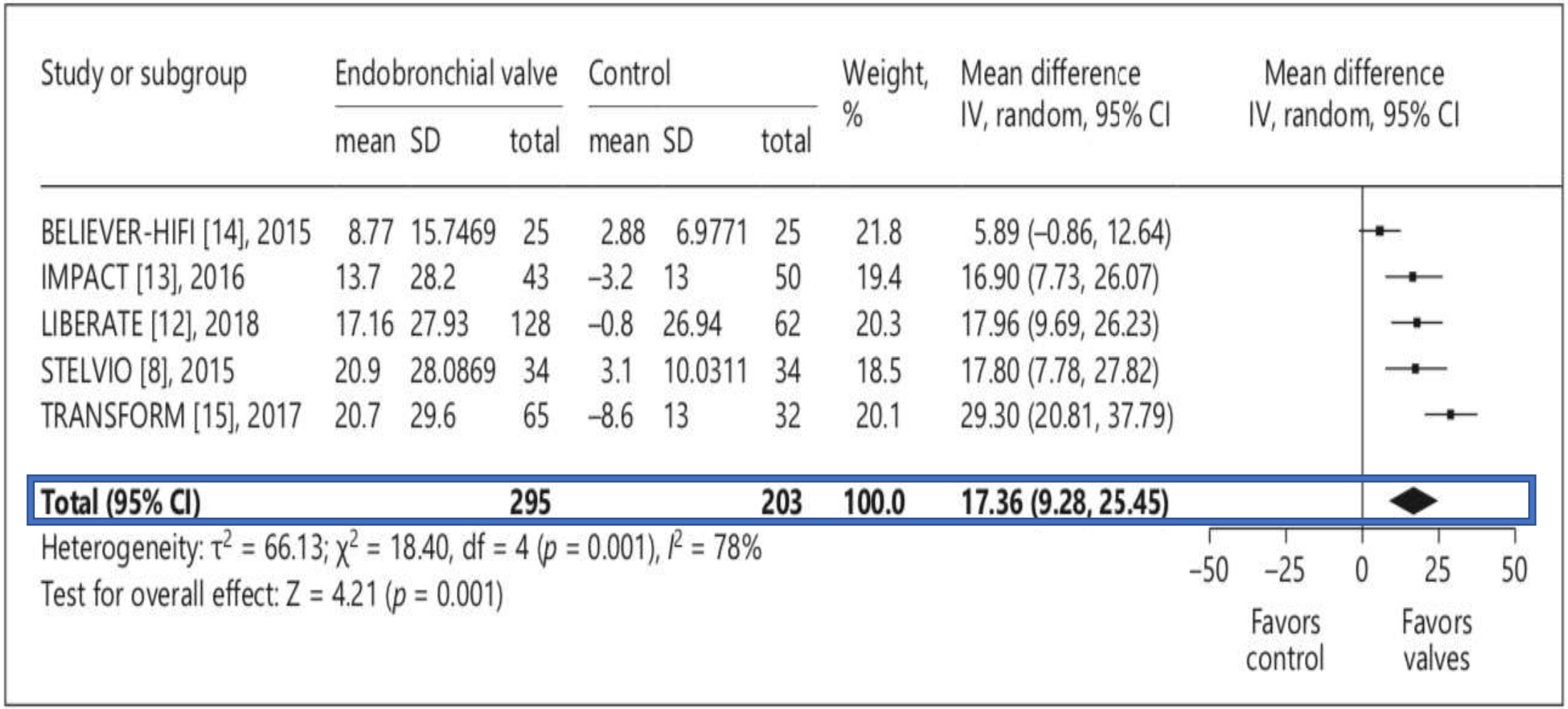

American journal of respiratory and critical care medicine. 2019 Dec 1;200(11):1354-62

# Bronchoscopic Lung Volume Reduction with Endobronchial Zephyr Valves for Severe Emphysema: A Systematic Review and Meta-Analysis

- 7 RCTs on Zephyr valves and 5 RCTs included only patients without collateral ventilation
- Seven studies with a total of 987 patients
- Five trials included only patients with complete fissures, and emphysema distribution was measured by Chartis®
- Four studies included heterogeneous emphysema (BELIEVER, TRANSFORM, and LIBERATE), 1 study both heterogeneous and homogeneous emphysema (STELVIO), and one study with homogeneous emphysema only (IMPACT)
- Changes in FEV1 % of predicted following Zephyr® EBV placement in patients without Collateral Ventilation evaluated in 5 studies

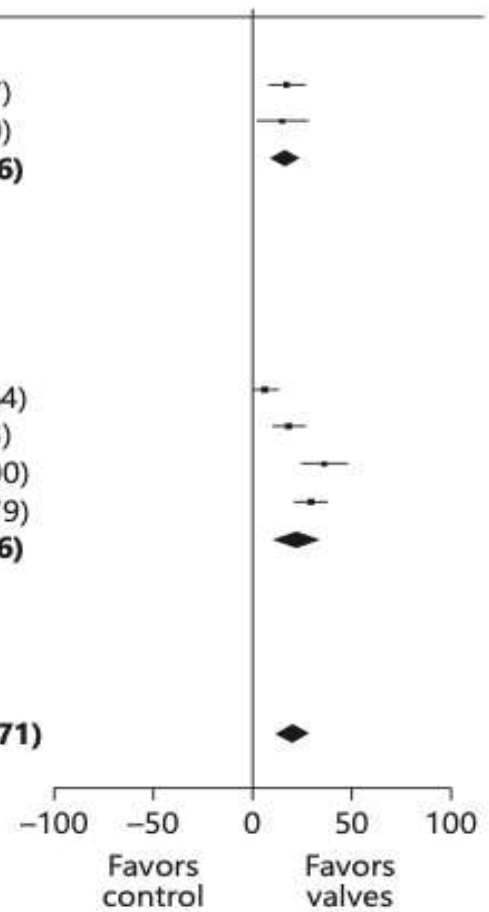
Respiration. 2019 May 22;98(3):268-78

Changes in FEV1 % of predicted following Zephyr® placement in patients without Collateral Ventilation




Respiration. 2019 May 22;98(3):268-78

| Study or subgroup | Endobronchial valve | | | Control | | | Weight, % | Mean difference IV, random (95% CI) | Mean difference IV, random, 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| | mean | SD | total | mean | SD | total | | | |
| **1.7.1 Homogeneous** | | | | | | | | | |
| IMPACT [13], 2016 | 13.7 | 28.2 | 43 | –3.2 | 13 | 50 | 17.0 | 16.90 (7.73, 26.07) | |
| STELVIO [8], 2015 | 20.1 | 19.8983 | 18 | 5.1 | 19.8983 | 18 | 14.4 | 15.00 (2.00, 28.00) | |
| **Subtotal (95% CI)** | | | **61** | | | **68** | **31.4** | **16.27 (8.78, 23.76)** | |
| Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.05$, df = 1 ($p = 0.81$), $I^2 = 0\%$ | | | | | | | | | |
| Test for overall effect: Z = 4.26 ($p < 0.0001$) | | | | | | | | | |
| **1.7.2 Heterogeneous** | | | | | | | | | |
| BELIEVER-HIFI [14], 2015 | 8.77 | 15.7469 | 25 | 2.88 | 6.9771 | 25 | 18.5 | 5.89 (–0.86, 12.64) | |
| LIBERATE [12], 2018 | 17.16 | 27.9 | 128 | –0.8 | 26.94 | 62 | 17.6 | 17.96 (9.69, 26.23) | |
| STELVIO [8], 2015 | 32.6 | 17.3172 | 16 | –3.4 | 17.3172 | 16 | 15.1 | 36.00 (24.00, 48.00) | |
| TRANSFORM [15], 2017 | 20.7 | 29.6 | 65 | –8.6 | 13 | 32 | 17.4 | 29.30 (20.81, 37.79) | |
| **Subtotal (95% CI)** | | | **234** | | | **135** | **68.6** | **21.78 (8.70, 34.86)** | |
| Heterogeneity: $\tau^2 = 157.10$; $\chi^2 = 27.79$, df = 3 ($p < 0.00001$), $I^2 = 89\%$ | | | | | | | | | |
| Test for overall effect: Z = 3.26 ($p = 0.001$) | | | | | | | | | |
| **Total (95% CI)** | | | **295** | | | **203** | **100.0** | **19.81 (10.92, 28.71)** | |
| Heterogeneity: $\tau^2 = 99.35$; $\chi^2 = 28.06$, df = 5 ($p < 0.0001$), $I^2 = 82\%$ | | | | | | | | | |
| Test for overall effect: Z = 4.36 ($p < 0.0001$) | | | | | | | | | |
| Test for subgroup differences: $\chi^2 = 0.51$, df = 1 ($p = 0.47$), $I^2 = 0\%$ | | | | | | | | | |

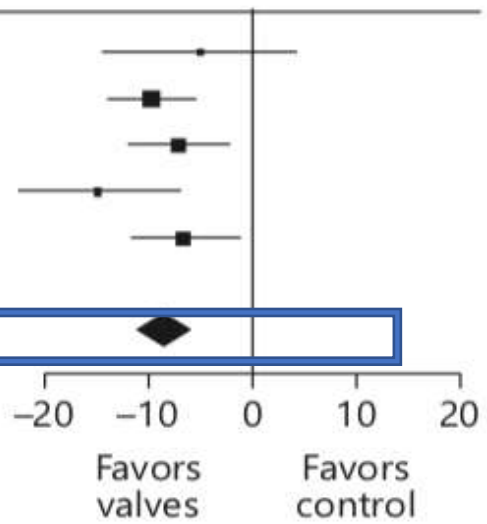



Respiration. 2019 May 22;98(3):268-78

Changes in the St George's Respiratory Questionnaire (total score) after intervention

| Study or subgroup | Endobronchial valve | | | Control | | | Weight, % | Mean difference IV, fixed (95% CI) |
|---|---|---|---|---|---|---|---|---|
| | mean | SD | total | mean | SD | total | | |
| BELIEVER-HIFI [14], 2015 | −8.63 | 20.8 | 25 | −3.66 | 11.2 | 25 | 7.0 | −4.97 (−14.23, 4.29) |
| IMPACT [13], 2016 | −8.63 | 11.2 | 43 | 1.01 | 9.3 | 50 | 33.5 | −9.64 (−13.87, −5.41) |
| LIBERATE [12], 2018 | −7.55 | 15.71 | 128 | −0.5 | 15.5 | 62 | 26.8 | −7.05 (−11.77, −2.33) |
| STELVIO [8], 2015 | −17.39 | 21.09 | 34 | −2.68 | 9.08 | 34 | 10.0 | −14.71 (−22.43, −6.99) |
| TRANSFORM [15], 2017 | −7.2 | 15.1 | 65 | −0.7 | 10.4 | 32 | 22.6 | −6.50 (−11.64, −1.36) |
| **Total (95% CI)** | | | **295** | | | **203** | **100.0** | **−8.42 (−10.86, −5.97)** |

Heterogeneity: $\chi^2 = 4.26$, df = 4 ($p = 0.37$), $I^2 = 6\%$
Test for overall effect: Z = 6.74 ($p < 0.00001$)



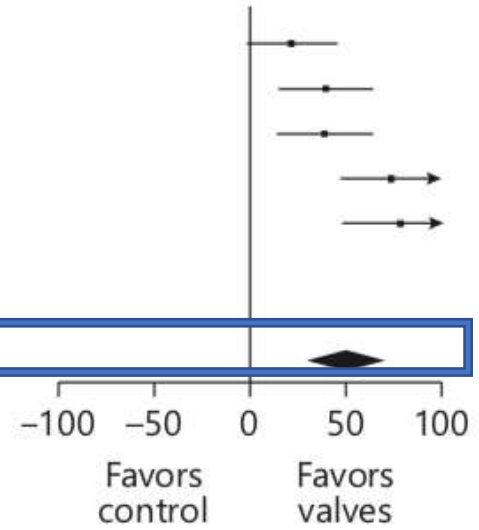

Respiration. 2019 May 22;98(3):268-78

Change in 6-min walking test (in meters) after intervention

| Study or subgroup | Endobronchial valve mean | SD | total | Control mean | SD | total | Weight, % | Mean difference IV, random (95% CI) |
|---|---|---|---|---|---|---|---|---|
| BELIEVER-HIFI [14], 2015 | 25 | 43.6 | 25 | 3 | 41.18 | 25 | 21.1 | 22.00 (–1.51, 45.51) |
| IMPACT [13], 2016 | 22.6 | 66.6 | 43 | –17.3 | 52.8 | 50 | 20.5 | 39.90 (15.19, 64.61) |
| LIBERATE [12], 2018 | 12.98 | 81.54 | 128 | –26.33 | 81.5 | 62 | 20.5 | 39.31 (14.59, 64.03) |
| STELVIO [8], 2015 | 60 | 71.65 | 34 | –14 | 31.52 | 34 | 19.8 | 74.00 (47.69, 100.31) |
| TRANSFORM [15], 2017 | 36.2 | 76.9 | 65 | –42.5 | 68.2 | 32 | 18.0 | 78.70 (48.57, 108.83) |
| **Total (95% CI)** | | | **295** | | | **203** | **100.0** | **49.75 (28.75, 70.75)** |

Heterogeneity: $\tau^2 = 400.00$; $\chi^2 = 13.32$, df = 4 ($p = 0.010$), $I^2 = 70\%$

Test for overall effect: Z = 4.64 ($p < 0.00001$)



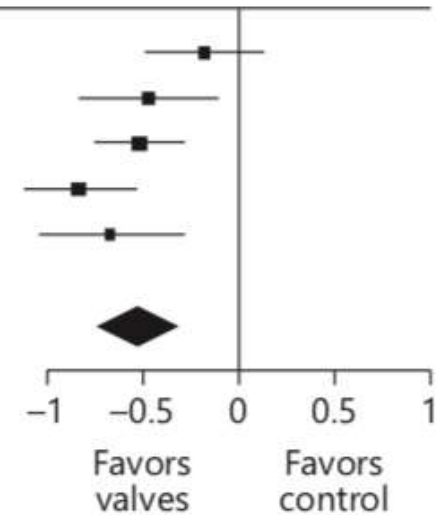

Respiration. 2019 May 22;98(3):268-78

Change in residual volume (in mL) after intervention

| Study or subgroup | Valve | | | Control | | | Weight, % | Mean difference IV, random (95% CI) |
|---|---|---|---|---|---|---|---|---|
| | mean | SD | total | mean | SD | total | | |
| BELIEVER-HIFI [14], 2015 | –0.26 | 0.2423 | 25 | –0.08 | 0.751 | 25 | 20.0 | –0.18 (–0.49, 0.13) |
| IMPACT [13], 2016 | –0.42 | 0.9 | 43 | 0.05 | 0.87 | 50 | 17.3 | –0.47 (–0.83, –0.11) |
| LIBERATE [12], 2018 | –0.49 | 0.83 | 112 | 0.03 | 0.66 | 62 | 24.9 | –0.52 (–0.74, –0.30) |
| STELVIO [8], 2015 | –0.865 | 0.6986 | 24 | –0.03 | 0.2538 | 33 | 20.9 | –0.83 (–1.13, –0.54) |
| TRANSFORM [15], 2017 | –0.66 | 1.04 | 65 | 0.01 | 0.79 | 32 | 16.8 | –0.67 (–1.04, –0.30) |
| **Total (95% CI)** | | | **269** | | | **202** | **100.0** | **–0.53 (–0.75, –0.32)** |

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 9.74$, df = 4 ($p = 0.04$), $I^2 = 59\%$

Test for overall effect: Z = 4.91 ($p < 0.00001$)



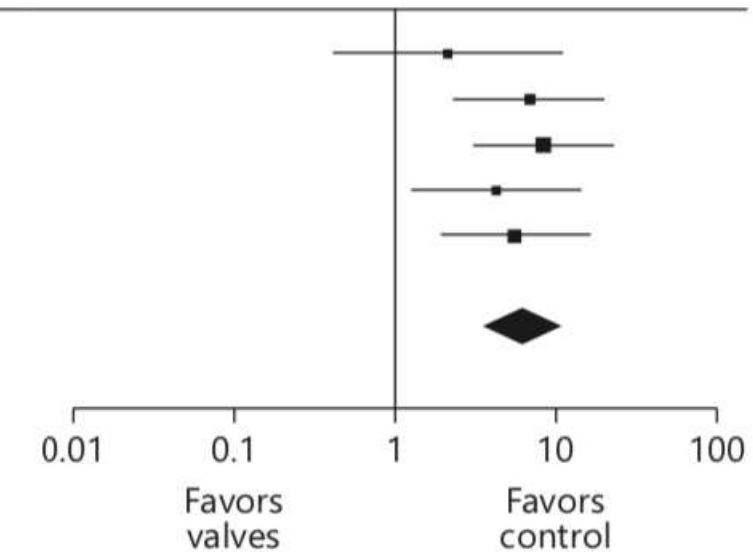

Respiration. 2019 May 22;98(3):268-78

Relative risk of pneumothorax after intervention

| Study or subgroup | Endobronchial valve events | Endobronchial valve total | Control events | Control total | Weight, % | Risk ratio M-H, fixed (95% CI) |
|---|---|---|---|---|---|---|
| BELIEVER-HIFI [14], 2015 | 2 | 23 | 4 | 100 | 11.0 | 2.17 (0.42, 11.16) |
| IMPACT [13], 2016 | 12 | 43 | 4 | 100 | 17.7 | 6.98 (2.38, 20.41) |
| LIBERATE [12], 2018 | 44 | 128 | 4 | 100 | 33.1 | 8.59 (3.19, 23.12) |
| STELVIO [8], 2015 | 6 | 34 | 4 | 100 | 15.0 | 4.41 (1.32, 14.70) |
| TRANSFORM [15], 2017 | 15 | 65 | 4 | 100 | 23.2 | 5.77 (2.00, 16.62) |
| **Total (95% CI)** | | **293** | | **500** | **100.0** | **6.32 (3.74, 10.67)** |
| **Total events** | **79** | | **20** | | | |

Heterogeneity: $\chi^2 = 2.41$, df = 4 ($p = 0.66$), $I^2 = 0\%$

Test for overall effect: Z = 6.89 ($p < 0.00001$)




Respiration. 2019 May 22;98(3):268-78

| Trial | Trial Characteristics | Fissure Integrity & Heterogenity | Follow up | FEV1 (ml) change | FEV1 (%) Change | 6Min Walk Test | SGRQ Change |
|---|---|---|---|---|---|---|---|
| VENT (2010) | Multicentre Prospective RCT (n=321) | Not specified | 6 months | NR | +16.2% | + 7.7% | NR |
| STELVIO (2015) | Prospective RCT | Enrolled Collateral ventilation | 6 months<br>12months | + 140ml<br>NR | + 17.8%<br>+17% | + 74m<br>+ 61m | −14.7<br>−11 |
| Be LieVer-HiFi (2015) | Single centre Double –blind , Sham – controlled RCT (n= 50) | Targeted heterogenous patients | 3 months | + 30 | + 5.9% | + 22 | -0.8 |
| IMPACT (2016) | Prospective Multicentre RCT (n=93) | Targeted Homogenous patients | 3 months | +120 | +16.9% | +40 | -7.6 |
| TRANSFORM (2017) | Prospective multicenter RCT (n=97) | Targeted heterogenous , collateral ventilation negative patients | 3 months | +230 | +29.3% | +78.7m | -6.5 |

| Trial | Trial characteristics | Fissure Integrity and Heterogenity | Follow up | FEV1(ml) Change | FEV1(%) Change | 6min Walk test | SGRQ Change |
|---|---|---|---|---|---|---|---|
| LIBERATE (2018) | Multicentre RCT (n= 190) | Targeted heterogenous, collateral ventilation patients | 12 months | +106 | +18% | +39.3m | -7.05 |
| REACH (2019) | Prospective multicentre unblinded RCT(n=107) | Targeted heterogenous, Collateral ventilation | 3 months | + 101 | NR | +19.7m | -7.19 |
| EMPROVE (2019) | Multicentre Prospective RCT (n= 172) | | 6 months | +101 | NR | +6.9m | - 13 |

# Endobronchial coils

# Lung Volume Reduction Coil Treatment vs Usual Care in Patients With Severe Emphysema -The REVOLENS Randomized Clinical Trial

- Multicentric RCT involving 100 patients
- 50 patients receive standard of care treatment
- Intervention group (n= 50) - standard treatment coil treatment within 15 days after randomization. The contralateral treatment completed 1 to 3 months after the first.
- Primary outcome improvement to atleast 54m in 6-minute walk test at 6 months
- Secondary outcomes - changes at 6 and 12 months in the 6-minute walk test, lung function, quality of life as assessed by St George's Respiratory Questionnaire, morbidity, mortality, total cost, and cost-effectiveness.

Jama. 2016 Jan 12;315(2):175-84

# Lung Volume Reduction Coil Treatment vs Usual Care in Patients With Severe Emphysema -The REVOLENS Randomized Clinical Trial

| Outcomes | Coil Treatment (n = 50) | Usual Care (n = 50) | Difference (1-Sided 95% CI) | *P* Value[a] |
|---|---|---|---|---|
| **Primary End Point** | | | | |
| 6-Minute walk test, ≥54 m improvement, No. (%)[b] | 18 (36) | 9 (18) | 0.18 (0.04 to ∞) | .03 |
| **Secondary End Points at 6 mo, Mean (95% CI)** | | | | |
| 6-Minute walk test improvement, m | 18 (−6 to 43) | −3 (−22 to 16) | 21 (−4 to ∞) | .06 |
| % Change | 9 (−1 to 20) | 1 (−6 to 9) | 8 (−2.7 to ∞) | .048 |
| Dyspnea | | | | |
| Modified Medical Research Council dyspnea scale score | −0.5 (−0.8 to −0.2) | −0.1 (−0.3 to 0.1) | −0.45 (−0.17 to −∞) | .01 |
| Transition Dyspnea Index total score[c] | 0.8 (−0.3 to 2.0) | −0.8 (−1.6 to 0) | 1.6 (0.54 to ∞) | .04 |
| Pulmonary function | | | | |
| $FEV_1$, L | 0.06 (0.02 to 0.11) | −0.03 (−0.05 to 0) | 0.09 (0.05 to ∞) | .001 |
| % Change | 9 (4 to 14) | −3 (−6 to 1) | 11 (6 to ∞) | .001 |
| FVC, L | 0.26 (0.11 to 0.40) | 0.05 (−0.12 to 0.22) | 0.21 (0.03 to ∞) | .03 |
| % Change | 15 (7 to 21) | 5 (−2 to 12) | 10 (1.5 to ∞) | .01 |
| RV, L | −0.52 (−0.74 to −0.31) | −0.15 (−0.41 to 0.11) | −0.37 (−0.09 to −∞) | .01 |
| % Change | −9 (−12 to −5) | −2 (−6 to 2) | −7 (−2 to −∞) | .009 |
| TLC, L | −0.34 (−0.50 to −0.18) | −0.14 (−0.35 to 0.06) | −0.20 (0.03 to −∞) | .09 |
| % Change | −4 (−6 to −2) | −2 (−4 to 1) | −2.0 (0.3 to −∞) | .10 |
| RV/TLC ratio | −0.04 (−0.05 to −0.02) | −0.01 (−0.03 to 0.01) | −0.03 (−0.01 to −∞) | .01 |
| % Change | −5 (−8 to −3) | −1 (−4 to 2) | −5.2 (−1.5 to −∞) | .01 |
| Quality of life | | | | |
| St George's Respiratory Questionnaire score | | | | |
| Total | −11.1 (−15.9 to −6.2) | 2.3 (−1.3 to 5.9) | −13.4 (−8 to −∞) | <.001 |
| Impact | −12.5 (−18.1 to −6.8) | 1.7 (−2.2 to 5.6) | −14.0 (−9 to −∞) | <.001 |
| Activity | −11.3 (−16.3 to −6.2) | 0.7 (−2.7 to 4.1) | −12.0 (−7 to −∞) | <.001 |
| Symptoms | −4.7 (−11.5 to 2.1) | 4.3 (−2.5 to 11.0) | −9.0 (−1.1 to −∞) | .04 |

Jama. 2016 Jan 12;315(2):175-84

# Lung Volume Reduction Coil Treatment vs Usual Care in Patients With Severe Emphysema -The REVOLENS Randomized Clinical Trial

| Secondary End Points at 12 mo, Mean (95% CI) | | | | |
|---|---|---|---|---|
| 6-Minute walk test improvement, m | −2 (−29 to 25) | −23 (−42 to −4) | 21 (−5 to ∞) | .12 |
| % Change | −0.05 (−10 to 10) | −7.2 (−13 to −1) | 7.1 (−2.2 to ∞) | .09 |
| Dyspnea | | | | |
| Modified Medical Research Council dyspnea scale score | −0.5 (−0.8 to −0.1) | −0.1 (−0.3 to −0.1) | −0.4 (−0.05 to −∞) | .02 |
| Transition Dyspnea Index total score[c] | −0.2 (−1.9 to 1.4) | −1.3 (−2.2 to −0.3) | 1.1 (−0.5 to ∞) | .08 |
| Pulmonary function | | | | |
| $FEV_1$, L | 0.05 (0.01 to −0.10) | −0.03 (−0.06 to 0.01) | 0.08 (0.03 to ∞) | .002 |
| % Change | 8 (3 to 13) | −3 (−8 to 2) | 11 (5.2 to ∞) | .002 |
| FVC, L | 0.27 (0.12 to 0.43) | 0 (−0.17 to 0.17) | 0.27 (0.07 to ∞) | .008 |
| % Change | 14 (7 to 21) | 4 (−3 to 9) | 10 (2.4 to ∞) | .02 |
| RV, L | −0.47 (−0.67 to −0.26) | −0.11 (−0.35 to 0.12) | −0.36 (−0.10 to −∞) | .004 |
| % Change | −9 (−12 to −5) | −2 (−5 to 1) | −7 (−2.6 to −∞) | .003 |
| TLC, L | −0.29 (−0.49 to −0.09) | −0.09 (−0.31 to 0.13) | −0.20 (0.04 to −∞) | .06 |
| % Change | −3 (−5 to −1) | −1 (−3 to 1) | −2 (0.3 to −∞) | .06 |
| RV/TLC ratio | −0.03 (−0.05 to −0.02) | 0 (−0.02 to 0.01) | −0.03 (−0.01 to −∞) | .007 |
| % Change | −5 (−7 to −2) | 0 (−3 to 2) | −5 (−1.6 to −∞) | .008 |
| Quality of life | | | | |
| St George's Respiratory Questionnaire score | | | | |
| Total | −9.1 (−14.1 to −4.2) | 1.5 (−1.8 to 4.7) | −10.6 (−5.8 to −∞) | <.001 |
| Impact | −10.8 (−16.4 to −5.1) | 1.8 (−2.5 to 6.0)) | −12.6 (−6.8 to −∞) | <.001 |
| Activity | −9.4 (−11.3 to −4.4) | 2.8 (0.0 to 5.6) | −12.2 (−7.5 to −∞) | <.001 |
| Symptoms | −4.2 (−11.5 to 3.0) | −3.9 (−8.7 to 0.9) | −0.3 (6.7 to −∞) | .45 |

Jama. 2016 Jan 12;315(2):175-84

| Changes from baseline | Heterogeneous[a] (n=17) | Homogeneous (n=33) | Difference (CI 95%) | P value |
|---|---|---|---|---|
| 6-minute walk test, m | +28 (-18;+75) | +13 (-17;+43) | 15 (-37 to +67) | .84 |
| % change | +10.8 (-7.1;+28.8) | +8.7 (-5.3;+22.7) | 2.1 (-19.1 to +23.3) | .88 |
| $FEV_1$, L | +0.04 (-0.03;+0.11) | +0.08 (+0.01;+0.14) | -0.04 (-0.12 to +0.05) | .38 |
| % change | +6 (-1;+15) | +10 (+3;+18) | -4 (-14 to +6) | .55 |
| FVC, L | +0.20 (-0.01;+0.41) | +0.29 (+0.08;+0.49) | -0.09 (-0.36 to +0.19) | .79 |
| % change | +14 (+2;+23) | +15 (+5;+24) | -2 (-15 to +12) | .99 |
| RV, L | -0.40 (-0.80;+0.01) | -0.55 (-0.80;-0.30) | 0.15 (-0.29 to +0.60) | .37 |
| % change | -6 (-12;-1) | -9 (-13;-5) | 3 (-4 to +9) | .43 |
| SGRQ, pts[b] | -12 (-19; -6) | -10 (-17;-3) | -2 (-11 to +7) | .83 |

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# Advantage

- Homogenous emphysema and  collateral ventilation

# Endobronchial Coil system versus Standard-of –care medical management in the treatment of subjects with severe emphysema

- Prospective, multicenter, open-label, randomized (2:1) controlled study
- Study participants ( n= 120)
- Endobronchial coil group (n=80) and control group (n= 40 patients)
- The first coil treatment was performed in 73 patients (91% of the 80 patients who were randomized for the coil treatment group) and 11 coils were placed.
- 64 patients bilaterally treated
- 11 coils used in second treatment

Respiration 2021;100:804–810

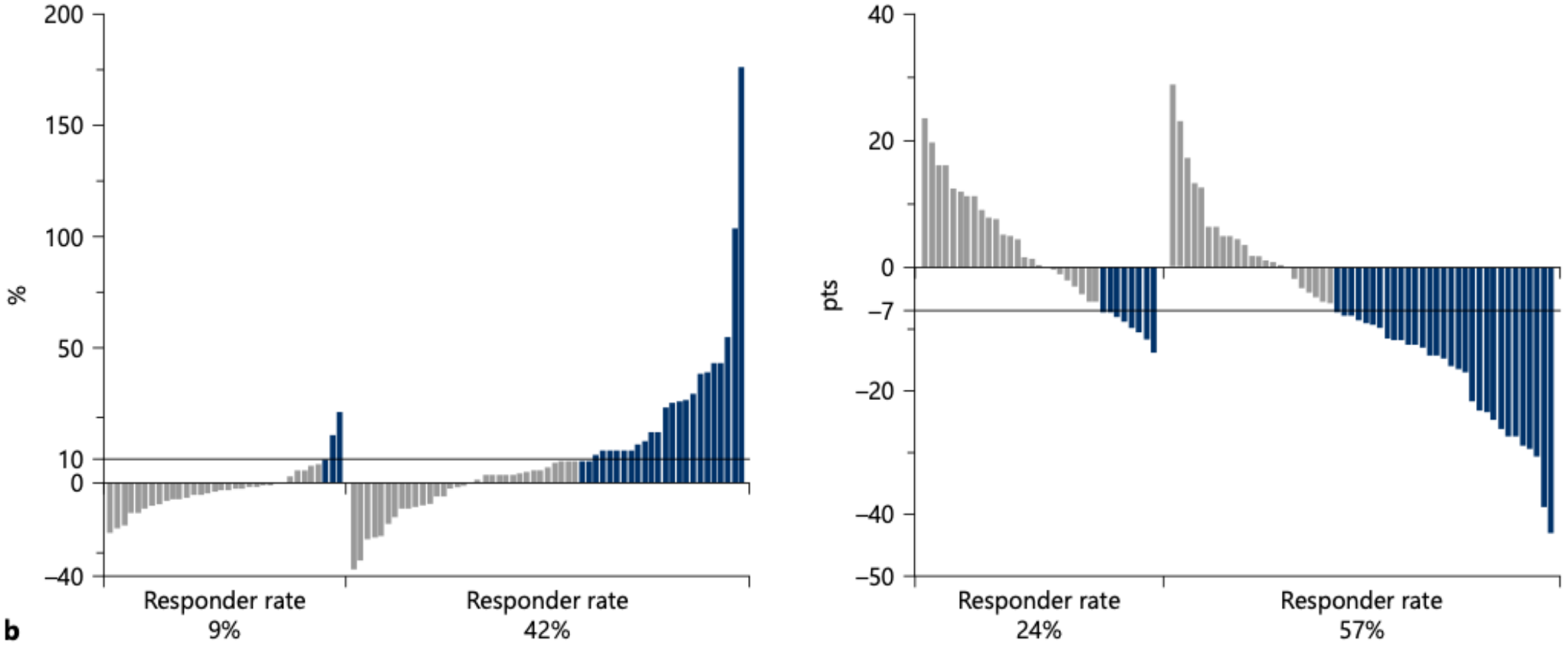
# Endobronchial Coil system versus Standard-of –care medical management in the treatment of subjects with severe emphysema

| Outcomes | Control | Treatment | Difference between groups | *p* value |
|---|---|---|---|---|
| Median change in $FEV_1$ | *n* = 34 | *n* = 57 | | |
| _mL | –20 (–45 to 0)<br>*p* = 0.055 | +40 (+15 to +90)<br>*p* = 0.006 | **+70 (+30 to +110)** | 0.001 |
| _% | –3.2 (–6.1 to –0.4)<br>*p* = 0.050 | +7.9 (+2.9 to +14.2)<br>*p* = 0.004 | **+10.3 (+4.7 to +16.0)** | 0.001 |
| Mean change in SGRQ | *n* = 33 | *n* = 54 | | |
| _points | +2.1 (–1.4 to +5.6)<br>*p* = 0.234 | –8.6 (–12.6 to –4.6)<br>*p* < 0.001 | **–10.6 (–15.9 to –5.4)** | <0.001 |

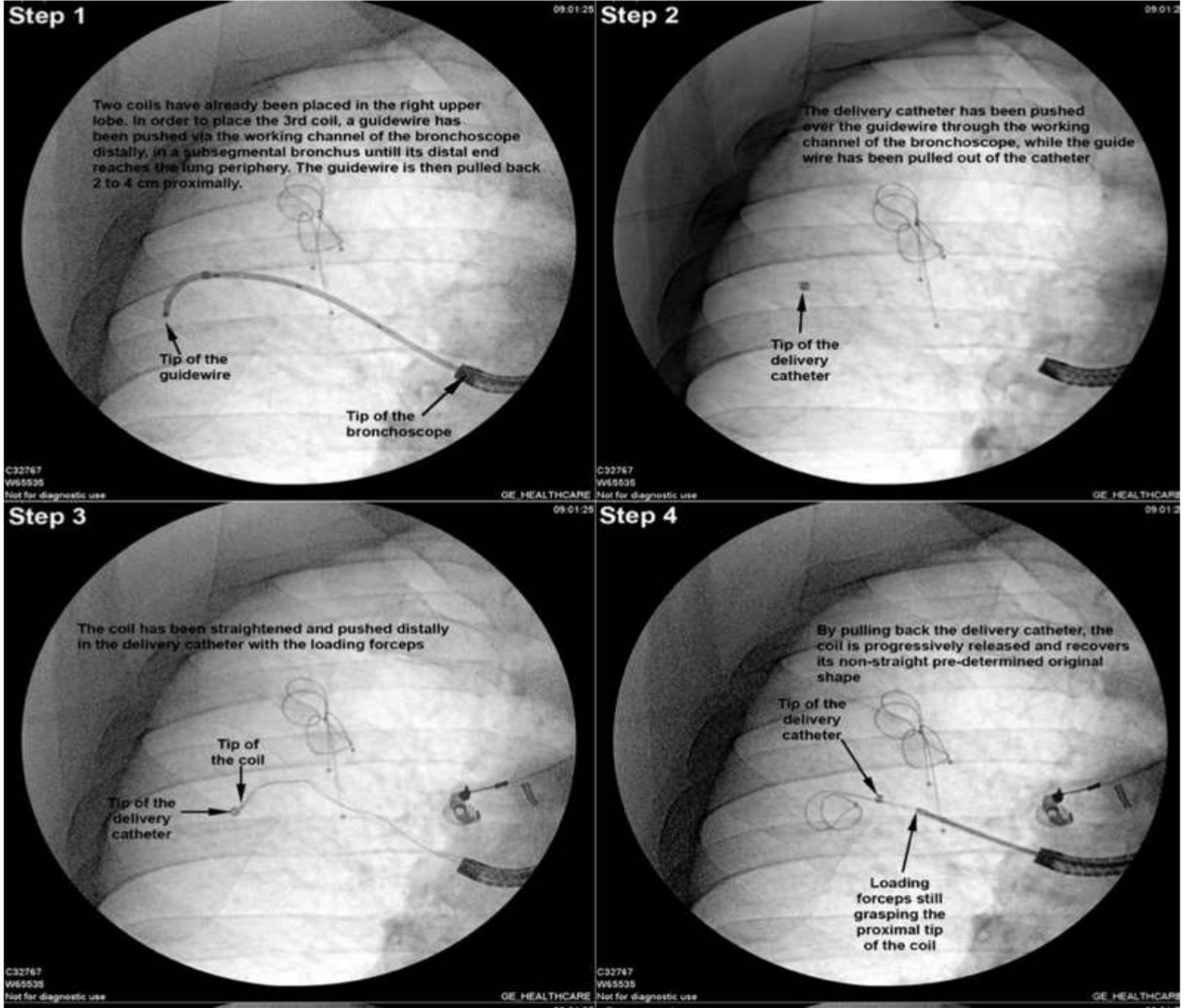
**a**


Respiration 2021;100:804–810

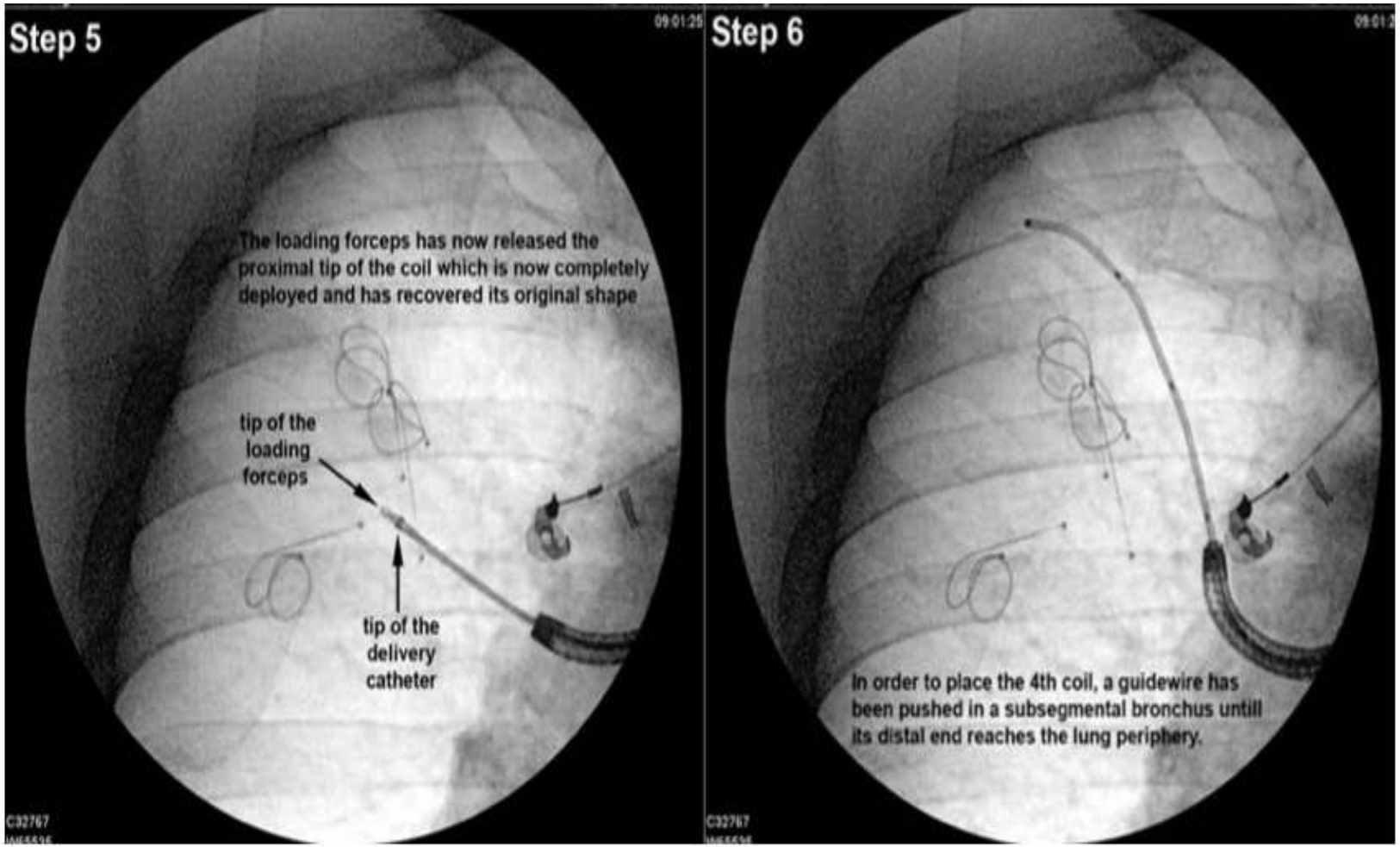
# Endobronchial Coil system versus Standard-of -care medical management in the treatment of subjects with severe emphysema




Respiration 2021;100:804–810




Jama. 2016 Jan 12;315(2):175-84




Jama. 2016 Jan 12;315(2):175-84

# Bronchoscopic Lung Volume Reduction with Valves and Coils A Network Meta-analysis

- 10 RCT - Valves (n =7) and coils (n=3)
- Zephry valves (n=5) and Spiration Valves (n= 2)
- Total of 1239 subjects (valves [n=777]; coils [n=462]; ZEPHYR valve [n=498]; SPIRATION valve: [n=279])

Annals of the American Thoracic Society. 2020 Nov;17(11):1468-75

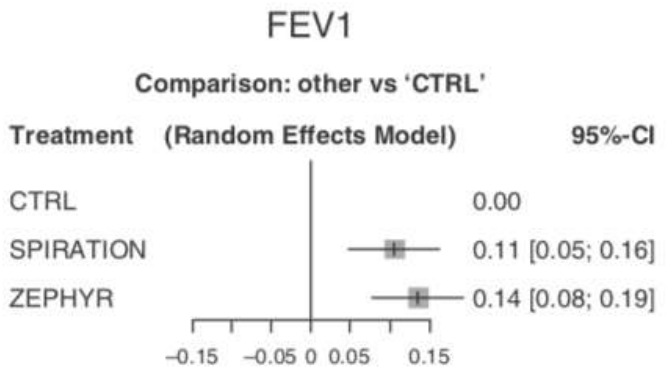
**Table 2.** Network meta-analysis results of the efficacy of valves in patients with heterogeneous emphysema with no collateral ventilation

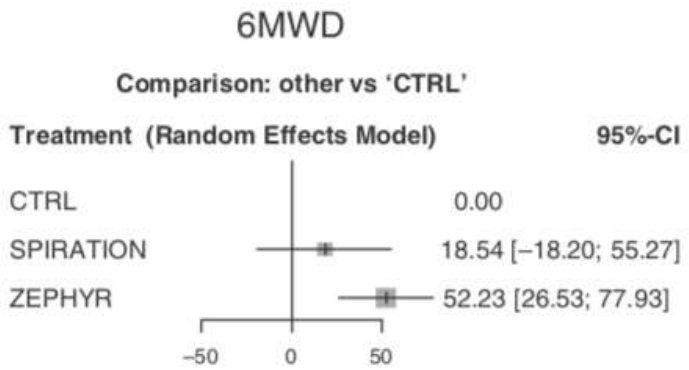
| | Network Meta-analysis Estimate (95% CI) | Studies Included in Comparison |
|---|---|---|
| $FEV_1$, L | | |
| Difference between Spiration and Control | 0.11 (0.05 to 0.16)* | EMOROVE, REACH |
| Difference between Zephyr and Control | 0.14 (0.08 to 0.19)* | BELIEVER-HIFI, LIBERATE, STELVIO, TRANSFORM |
| Difference between Zephyr and Spiration | 0.03 (−0.05 to 0.11) | BELIEVER-HIFI, LIBERATE, STELVIO, TRANSFORM, EMOROVE, REACH |
| 6MWD, m | | |
| Difference between Spiration and Control | 18.54 (−18.20 to 55.27) | EMOROVE, REACH |
| Difference between Zephyr and Control | 52.23 (26.53 to 77.93)* | BELIEVER-HIFI, LIBERATE, STELVIO, TRANSFORM |
| Difference between Zephyr and Spiration | 33.69 (−11.14 to 78.53) | BELIEVER-HIFI, LIBERATE, STELVIO, TRANSFORM, EMOROVE, REACH |
| SGRQ | | |
| Difference between Spiration and Control | −9.32 (−14.18 to −4.45)* | EMOROVE, REACH |
| Difference between Zephyr and Control | −8.14 (−11.94 to −4.35)* | BELIEVER-HIFI, LIBERATE, STELVIO, TRANSFORM |
| Difference between Zephyr and Spiration | −1.17 (−7.35 to 5.00) | BELIEVER-HIFI, LIBERATE, STELVIO, TRANSFORM, EMOROVE, REACH |
| Pneumothorax, odds ratio | | |
| Spiration vs. Control | 10.32 (1.35 to 79.13)* | EMOROVE, REACH |
| Zephyr vs. Control | 11.47 (2.91 to 45.27)* | BELIEVER-HIFI, LIBERATE, STELVIO, TRANSFORM |
| Zephyr vs. Spiration | 1.11 (0.09 to 12.9) | BELIEVER-HIFI, LIBERATE, STELVIO, TRANSFORM, EMOROVE, REACH |
| COPD exacerbation, odds ratio | | |
| Spiration vs. Control | 2.04 (0.88 to 4.74) | EMOROVE, REACH |
| Zephyr vs. Control | 1.56 (0.72 to 3.38) | BELIEVER-HIFI, LIBERATE, STELVIO, TRANSFORM |
| Zephyr vs. Spiration | 0.74 (0.24 to 2.40) | BELIEVER-HIFI, LIBERATE, STELVIO, TRANSFORM, EMOROVE, REACH |

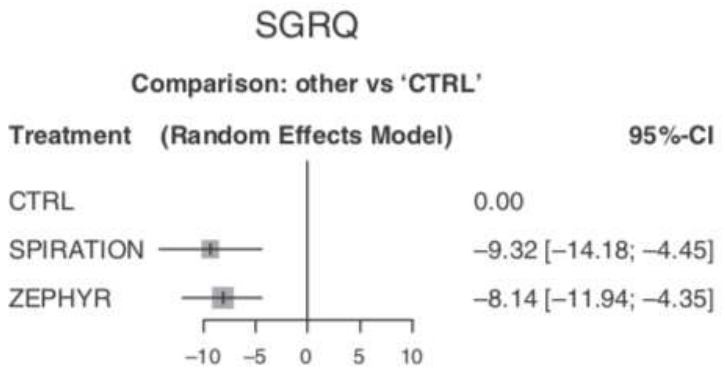
*Definition of abbreviations*: 6MWD = 6-minute walk distance; CI = confidence interval; COPD = chronic obstructive pulmonary disease; $FEV_1$ = forced expiratory volume in 1 second reported in liters; SGRQ = St. George's Respiratory Questionnaire score.
Both direct and indirect estimates were similar and reported as network meta-analysis estimate.
*Statistically significant

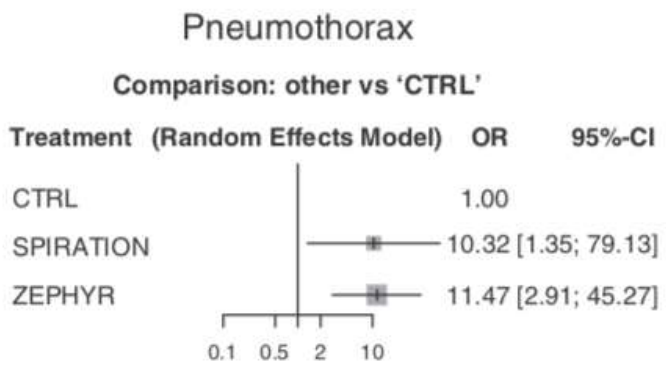
Annals of the American Thoracic Society. 2020 Nov;17(11):1468-75

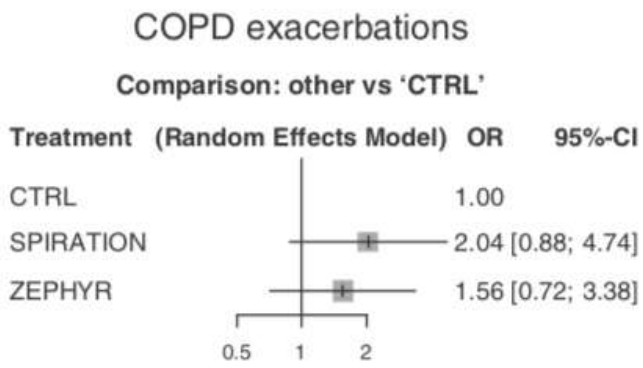
Forest plots for network meta-analysis of valves in patients with heterogeneous emphysema with no collateral ventilation



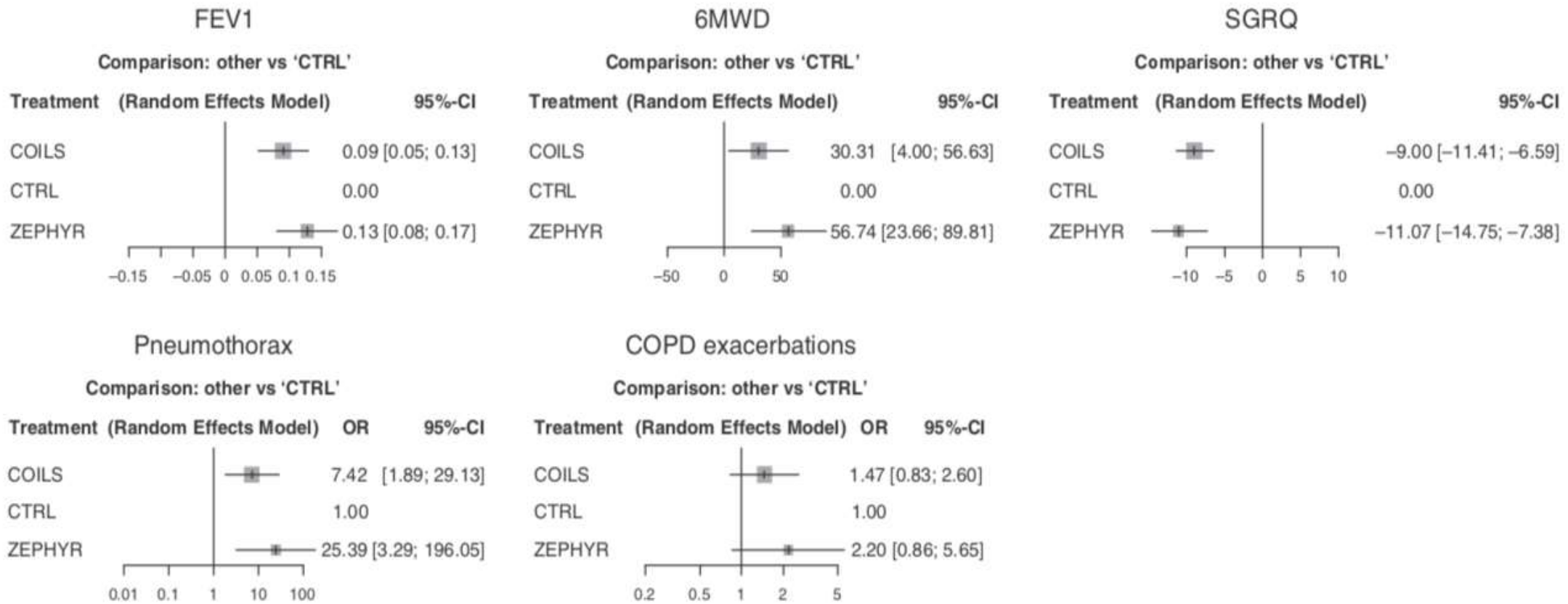




Annals of the American Thoracic Society. 2020 Nov;17(11):1468-75

Forest plots for network meta-analysis of valves in patients with heterogeneous and homogenous emphysema with no collateral ventilation




Annals of the American Thoracic Society. 2020 Nov;17(11):1468-75

# Thermal Vapor Ablation

- Instillation of heated water vapor ( thermal energy) to a target pulmonary segment to induce local inflammatory reaction - scarring, fibrosis, and eventual volume loss in order to reduce hyperinflation

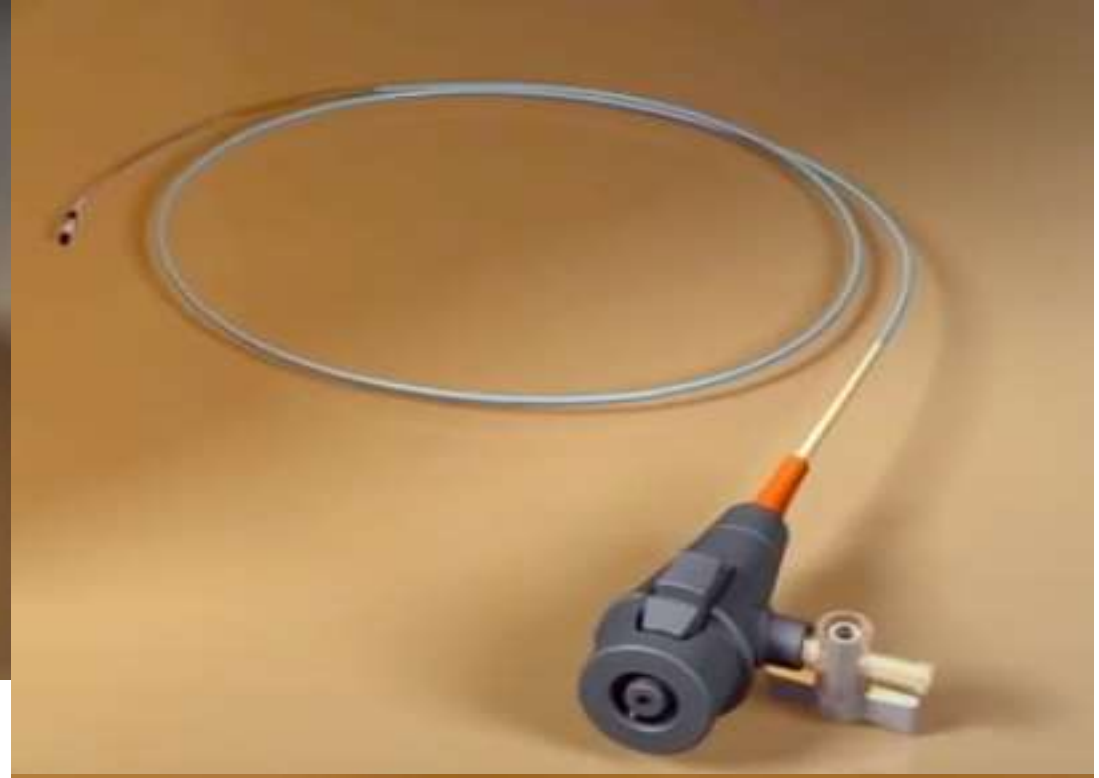
- **Contraindications**
- Bronchial asthma, chronic bronchitis and bronchiectasis
- Patients with cardiovascular or pulmonary vascular disease

Lancet Respir Med. 2016 Mar;4(3):185-93

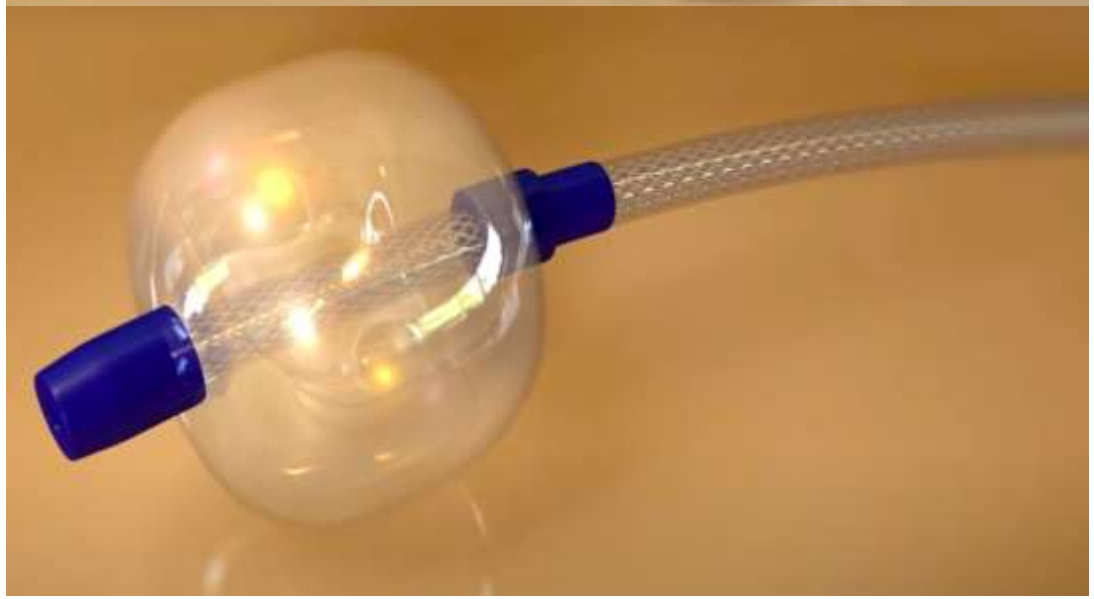
# Thermal Vapor Ablation

- Vapor dose is calculated based on the volume and density of the targeted lung tissue to be treated via a proprietary software (Uptake Medical Corporation, Seattle, WA, USA)

Lancet Respir Med. 2016 Mar;4(3):185-93




First Segment: RB2 (Posterior)
Right Upper Lobe
Preferred treatment location: Segmental Level
Treating
NEXT



# Segmental volume reduction using thermal vapour ablation in patients with severe emphysema - STEP-UP trial

- Multicentre, parallel-group, randomised (2:1), controlled, open-label trial - 13 hospital sites in Europe (ten sites) and Australia (three sites)
- Sequential Staged Treatment of Emphysema with Upper Lobe Predominance (STEP-UP) trial
- Study participants (n=70)
- Randomization (2:1), 46 to the treatment group and 24 to the control group
- Intervention – Heated water vapor delivered via bronchoscopy within 1 week of screening visit and second treatment session given 13 weeks after the first treatment session

Lancet Respir Med. 2016 Mar;4(3):185-93

# Segmental volume reduction using thermal vapour ablation in patients with severe emphysema - STEP-UP trial

- Primary efficacy endpoints - change in FEV1 and SGRQ-C scores between the treatment and control at 6 months
- Secondary end points – change in 6min walk distance in metres, FEV1, FVC , Total lung capacity(ml), residual volume (ml) and Functional residual capacity (ml) at 6 months

Lancet Respir Med. 2016 Mar;4(3):185-93

# Segmental volume reduction using thermal vapour ablation in patients with severe emphysema - STEP-UP trial

| | Bronchoscopic vapour ablation group | | Control group | | Difference between groups (95% CI) | p value |
|---|---|---|---|---|---|---|
| | Patients, n | Mean (SD) | Patients, n | Mean (SD) | | |
| **$FEV_1$, %** | | | | | | |
| 3 months* | 43 | 8·2% (17·5%) | 22 | −1·8% (10·1%) | 10·1% (3·2 to 16·9) | 0·0047 |
| 6 months | 41 | 11·0% (16·2%) | 23 | −3·7% (11·1%) | 14·7% (7·8 to 21·5) | <0·0001 |
| **SGRQ-C, points** | | | | | | |
| 3 months* | 44 | −7·2 (12·2%) | 22 | −0·6 (11·0) | −6·6 (−12·4 to −0·9) | 0·0243 |
| 6 months | 42 | −9·7 (14·4) | 23 | −0·0 (9·8) | −9·7 (−15·7 to −3·7) | 0·0021 |

$FEV_1$=forced expiratory volume in 1 s. SGRQ=St George's Respiratory Questionnaire. *3-month data were collected before the second treatment session was administered.

***Table 3*: Results for primary efficacy endpoints**

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# Segmental volume reduction using thermal vapour ablation in patients with severe emphysema - STEP-UP trial

| | 3 months* | | 6 months | |
|---|---|---|---|---|
| | Absolute difference between groups (95% CI) | p value | Absolute difference between groups (95% CI) | p value |
| 6MWT, m | 29·4 (−3·1 to 61·8) | 0·0748 | 30·5 (−1·5 to 62·4) | 0·0614 |
| $FEV_1$, mL | 80·5 (18·6 to 142·4) | 0·0117 | 130·8 (63·6 to 198·0) | 0·0002 |
| Forced vital capacity, mL | 163·7 (−15·1 to 342·5) | 0·0717 | 243·1 (57·0 to 429·3) | 0·0115 |
| Total lung capacity, mL | −2·4 (−233·0 to 228·1) | 0·9832 | −77·6 (−313·6 to 158·4) | 0·5111 |
| Residual volume, mL | −44·1 (−305·9 to 217·7) | 0·7374 | −302·5 (−542·6 to −62·4) | 0·0145 |
| Functional residual capacity (thoracic gas volume), mL | −35·4 (−288·9 to 218·0) | 0·7809 | −130·9 (−368·9 to 107·2) | 0·2758 |

6MWT=6-min walk test. $FEV_1$=forced expiratory volume in 1 s. *3-month data were collected before completion of the second treatment session.

***Table 4*: Absolute difference between trial groups at 3 and 6 months for secondary efficacy endpoints**

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# Segmental volume reduction using thermal vapour ablation in patients with severe emphysema - STEP-UP trial

| | Treatment group (n=45) | | | Control group (n=24) |
|---|---|---|---|---|
| | After treatment session 1 | After treatment session 2 | 0–180 days of treatment (overall)* | 0–180 days of randomisation (overall) |
| COPD exacerbation | 6 (13%) | 6 (15%) | 11 (24%) | 1 (4%) |
| Pneumonia or pneumonitis | 6 (13%) | 3 (8%) | 8 (18%) | 2 (8%) |
| Pneumothorax | 0 | 1 (3%) | 1 (2%) | 0 |
| Requiring surgery | 0 | 0 | 0 | 0 |
| Requiring chest tube(s) | 0 | 0 | 0 | 0 |
| Haemoptysis | 0 | 1 (3%) | 1 (2%) | 0 |
| Death | 1 (2%) | 0 | 1 (2%) | 0 |
| Any serious respiratory adverse event | 10 (22%) | 9 (23%) | 16 (36%) | 3 (13%) |

Data are n (%). *180 days after treatment session 1 or 90 days after treatment session 2.

Lancet Respir Med. 2016 Mar;4(3):185-93

# Advantages

- Heterogenous upper lobe  emphysema with and with out collateral ventilation

Lancet Respir Med. 2016 Mar;4(3):185-93

# Biologic Lung Reduction

- Bronchoscopic instillation of a substance (sealants, adhesives, and autologous blood) induces an inflammatory reaction with subsequent remodelling of lung parenchyma, formation of fibrosis, and contracture
- Autologous blood mixed with cyklokapron and calcium chloride
- Aeri Seal – (glutaraldehyde ) commonly used

# A randomised trial of lung sealant versus medical therapy for advanced emphysema

- Multicentric randomized controlled trial
- Study participants (n=95)
- 61 patients randomised to ELS group ; 34 to control treatment
- Intervention - two upper lobe sub-segments in each lung  treated in a single session
- Primary efficacy end-point - mean percentage change in post-bronchodilator FEV1 from baseline to 12 months
-

European Respiratory Journal. 2015 Sep 1;46(3):651-62

# A randomised trial of lung sealant versus medical therapy for advanced emphysema

- Secondary efficacy end-points:
- Proportion of patients achieving minimal clinically important differences (MCID) in FEV1 (MCID ⩾100 mL and 12%)
- Dyspnoea - modified Medical Research Council dyspnoea scale (mMRC) (0–4, a higher score indicating more severe dyspnoea and MCID ⩾1 U decrease)
- Disease-specific quality of life measured by St George's Respiratory Questionnaire (SGRQ) (0–100: a higher score indicating worse quality of life and MCID ⩾4 U decrease
- Changes in 6MWD and upper lobe volume (measured by quantitative CT) at 12 months.

European Respiratory Journal. 2015 Sep 1;46(3):651-62

# A randomised trial of lung sealant versus medical therapy for advanced emphysema

| Primary outcome<br>At 6 months | Treatment group | Control group |
|---|---|---|
| Change in FEV1 %<br>& ml | 18.9% (-0.7–41.9%) &<br>100 mL (0–370 ml) | 1.3% (-8.2–12.9%)<br>& 10 mL (-90–100 mL) |

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 |

European Respiratory Journal. 2015 Sep 1;46(3):651-62

| | 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) | | | | | | | |
| Myocardial infarction | | | 1 (1) | | | | | |
| Chest pain | | | 1 (1) | | | | | |
| Tachyarrhythmia | | | | | | | 1 (1) | 1 (1) |
| Sepsis | | | 1 (1) | | 1 (1) | | | |
| Fever | | | 1 (1) | | | | | |
| Acute kidney injury | | | 1 (1) | | | | | |
| Urinary tract infection | | | | | 1 (1) | | 1 (1) | |
| Ileus | | | 1 (1) | | | | | |
| Inguinal hernia | | | | | | | 1 (1) | |
| Depression | | | 1 (1) | | | | | |

European Respiratory Journal. 2015 Sep 1;46(3):651-62

# Airway Bypass Stents

- Exhale® Airway Bypass Procedure (Bronchus Technologies, Mountain View, CA, USA) uses expandable silicone- coated, paclitaxel-eluting stents placed endobronchially into emphysematous lung tissue to enhance the emptying of trapped air and hence, achieving lung volume reduction.

The Lancet. 2011 Sep 10;378(9795):997-1005

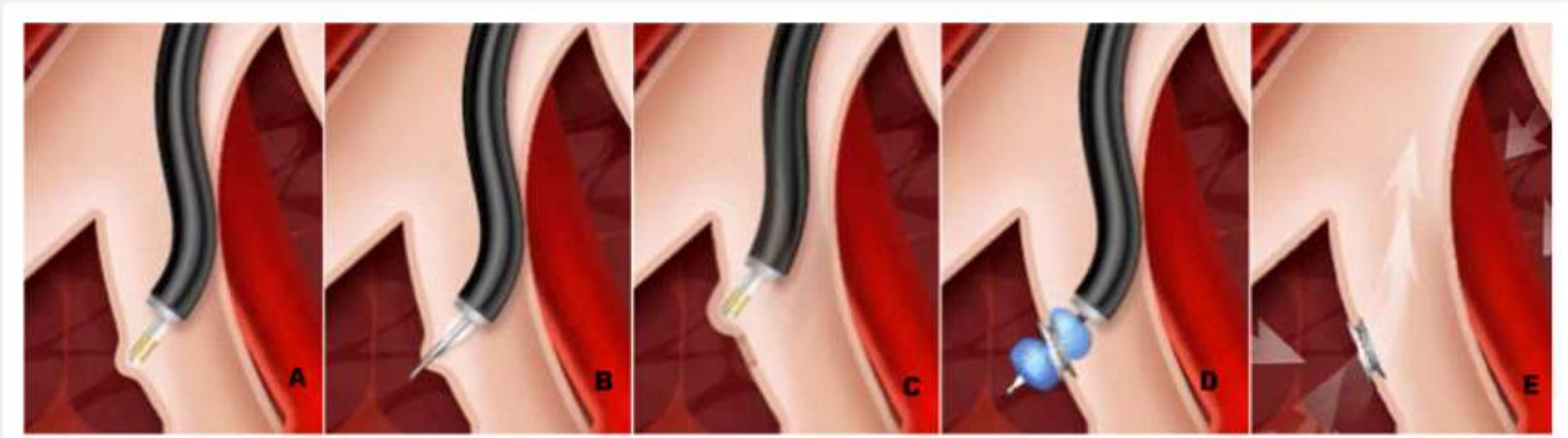
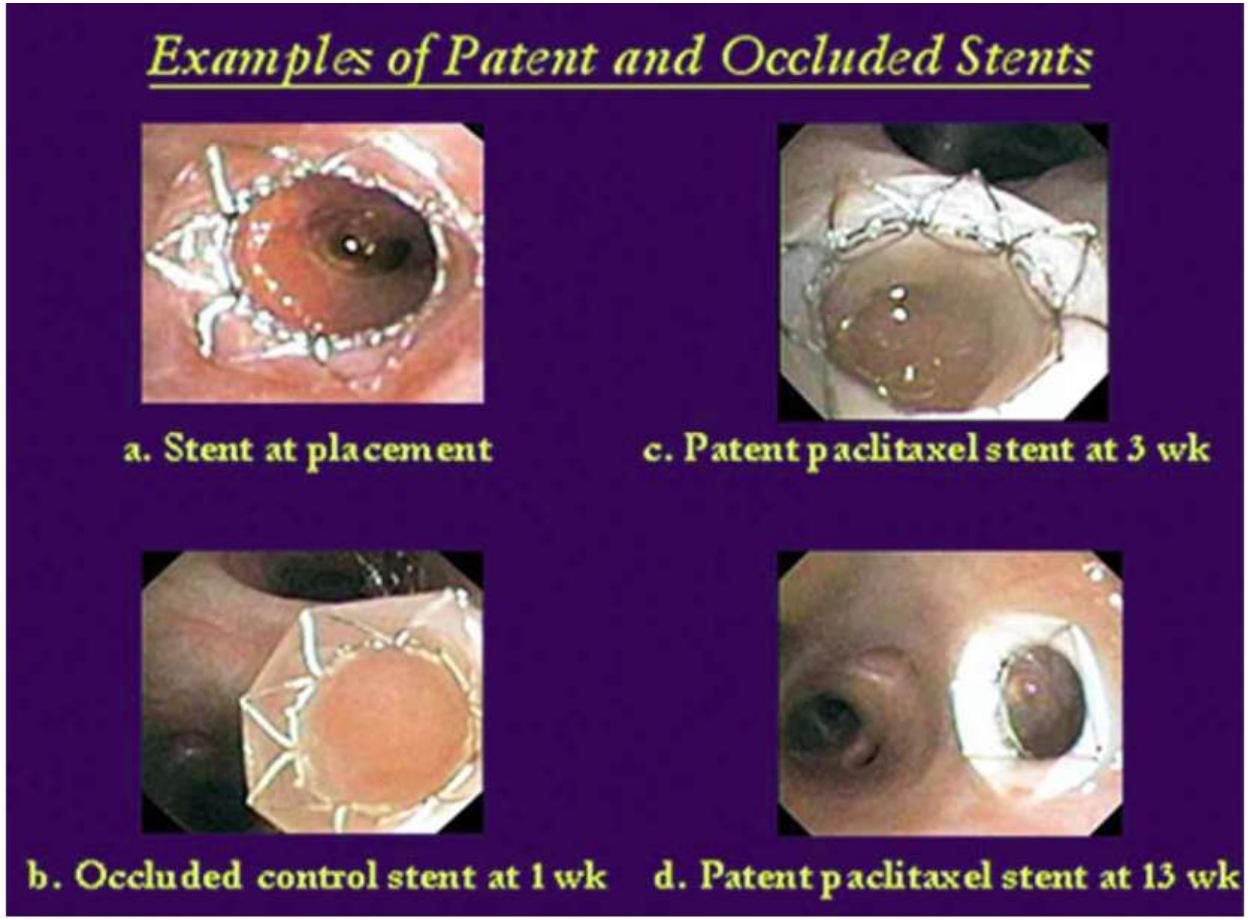



**Figure 2**

Schematic representations of airway bypass using EXHALE airway stents.
From left to right: A- identification of a blood vessel– free location with a Doppler probe at the level of segmental bronchi; B- fenestration of the bronchial wall using the transbronchial needle; C- confirmation with Doppler; D- using dilating balloon through the fenestration; E- placement of a stent to hold the passage open.

The Journal of thoracic and cardiovascular surgery. 2006 Jan 1;131(1):60-4




The Journal of thoracic and cardiovascular surgery. 2006 Jan 1;131(1):60-4

# Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial)

- Randomised, double-blind, sham-controlled study involving 38 specialist respiratory centres
- Study Participants (n= 315)
- Airway bypass (n=208) or sham control (107)
- Intervention - airway bypass, passages were created and up to six stents placed (maximum of two stents per lobe, excluding the right middle lobe) per individual.
- The co-primary efficacy endpoint if FVC increased by at least 12% and modified Medical Research Council dyspnoea score (mMRC; table 2) fell by 1 point from baseline at the 6-month follow-up visit and the primary safety end point

The Lancet. 2011 Sep 10;378(9795):997-1005

# Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial)

- Secondary efficacy endpoints included
- Change in Residual volume, Total lung capacity, RV/TLC, FVC, and forced expiratory volume in 1 s (FEV1)
- St George's respiratory questionnaire (SGRQ)
- 6-min walk test;
- Endurance cycle ergometry, set to 75% of maximum workload.

The Lancet. 2011 Sep 10;378(9795):997-1005

| | Day 1 | Month 1 | Month 3 | Month 6 | Month 12 |
|---|---|---|---|---|---|
| **Co-primary efficacy endpoints** | | | | | |
| FVC (L) | | | | | |
| Airway bypass | 0·27 (0·6) | 0·06 (0·4) | 0·02 (0·4) | −0·03 (0·4) | −0·08 (0·5) |
| Control | 0·00 (0·4) | 0·02 (0·3) | 0·04 (0·3) | −0·04 (0·4) | 0·00 (0·4) |
| p value* | <0·001 | 0·329 | 0·551 | 0·870 | 0·208 |
| mMRC (0–4) | | | | | |
| Airway bypass | −0·41 (0·9) | −0·63 (1·0) | −0·53 (0·9) | −0·47 (1·0) | −0·41 (1·0) |
| Control | −0·41 (0·8) | −0·43(0·9) | −0·42 (0·9) | −0·22 (0·9) | −0·25 (1·0) |
| p value* | 0·960 | 0·085 | 0·357 | 0·045 | 0·212 |
| **Pulmonary function endpoints** | | | | | |
| RV (L) | | | | | |
| Airway bypass | −0·38 (0·8) | −0·15 (0·6) | −0·12 (0·6) | −0·061 (0·7) | −0·06 (0·7) |
| Control | −0·12 (0·6) | 0·01 (0·7) | −0·14 (0·6) | 0·03 (0·5) | −0·10 (0·6) |
| p value* | 0·017 | 0·083 | 0·803 | 0·705 | 0·718 |
| RV (% predicted) | | | | | |
| Airway bypass | −17·9 (38) | −6·8 (29) | −6·0 (29) | −4·7 (31) | −5·6 (32) |
| Control | −5·8 (25) | −1·2 (31) | −7·5 (26) | −3·7 (25) | −7·4 (27) |
| p value* | 0·016 | 0·121 | 0·654 | 0·781 | 0·677 |
| $FEV_1$ (L) | | | | | |
| Airway bypass | 0·09 (0·2) | 0·02 (0·1) | 0·01 (0·1) | −0·01 (0·1) | −0·02 (0·2) |
| Control | 0·00 (0·1) | 0·01 (0·1) | −0·01 (0·1) | −0·02 (0·1) | −0·04 (0·1) |
| p value* | <0·001 | 0·217 | 0·110 | 0·406 | 0·186 |
| $FEV_1$ (% predicted) | | | | | |
| Airway bypass | 3·1 (6) | 0·7 (4) | 0·3 (4) | −0·3 (4) | −0·15 (7) |
| Control | 0·1 (3) | 0·3 (3) | −0·2 (3) | −0·6 (3) | −1·1 (3) |
| p value* | <0·001 | 0·277 | 0·231 | 0·445 | 0·269 |

The Lancet. 2011 Sep 10;378(9795):997-1005

| | Airway bypass (n=208) | Sham control (n=107) |
|---|---|---|
| Participants having a composite safety event | 30 (14·4%) | 12 (11·2%) |
| Respiratory failure requiring mechanical ventilation for 24 h or longer | 4 (1·9%) | 0 (0%) |
| Pneumothorax requiring intercostal tube drainage for more than 7 days | 2 (1·0%) | 0 (0%) |
| Major haemoptysis | 1 (0·5%) | 0 (0%) |
| COPD or infection needing admission for longer than 7 days | 22 (10·6%) | 9 (8·4%) |
| Death at 30 days or earlier and respiratory death after 30 days | 4 (1·9%) | 4 (3·7%) |

The Lancet. 2011 Sep 10;378(9795):997-1005

# Disadvantages

- More serious adverse events
- Short duration of benefit both in primary and secondary endpoints (returned to baseline within 6 months)

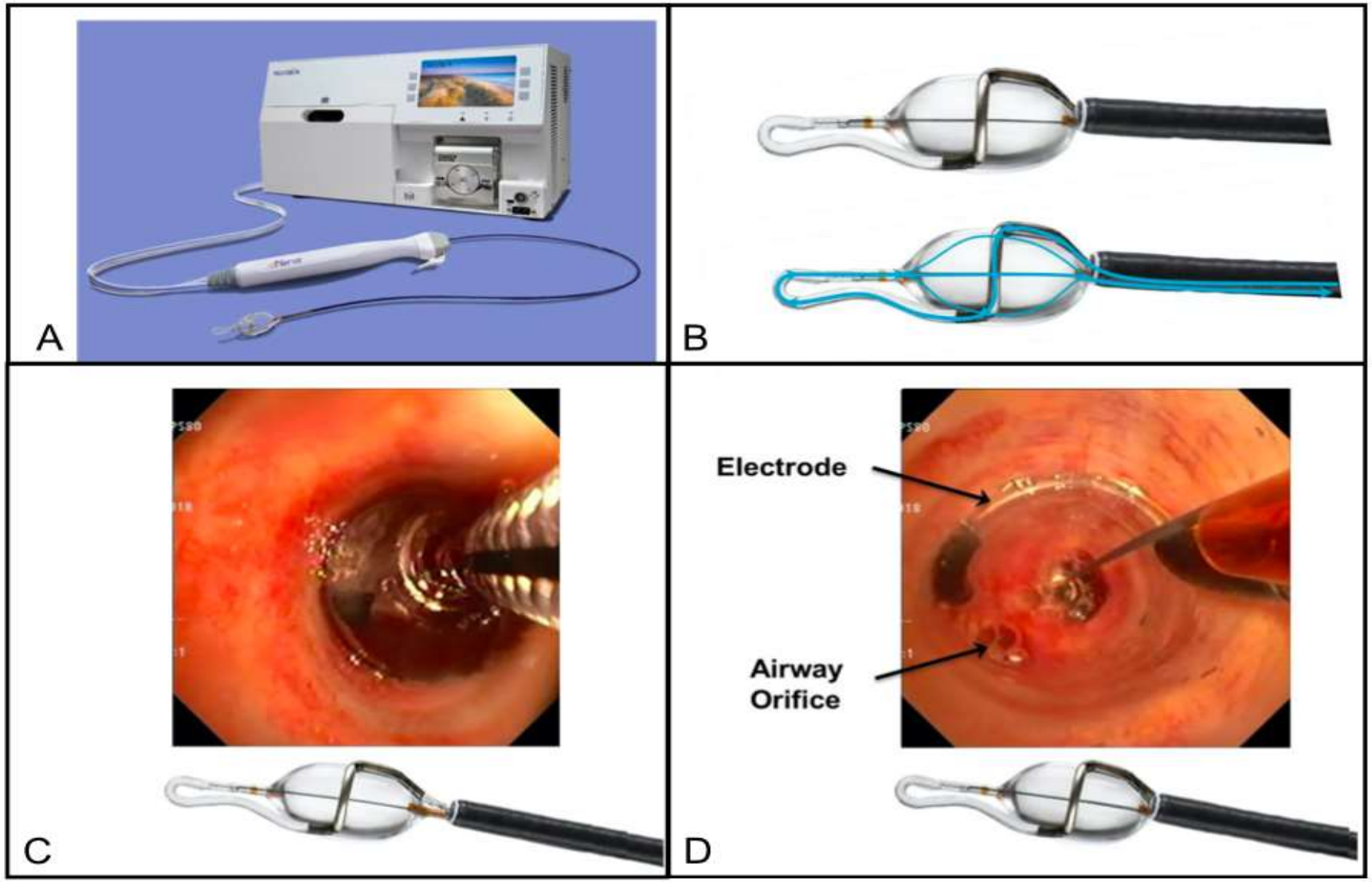
The Lancet. 2011 Sep 10;378(9795):997-1005

# Therapy for Mucus hypersecretion and inflammation

# Targeted Lung Denervation

- Aimed at attenuating parasympathetic overactivity by disrupting peribronchial vagal innervation of the lung to reduce bronchoconstriction and mucus hypersecretion
- Radiofrequency energy is delivered via a double-cooled catheter (Nuvaira, Minneapolis, MN, USA) to produce a narrow band of ablation around the main bronchi while minimizing the effect to the inner surface of the airway.
- Targeted nerve fibers are disconnected from their proximal segments due to thermal injury, and subsequent wallerian degeneration degrades distal fibers out to peripheral endings along small airways with persistent cessation of acetylcholine release

American Journal of Respiratory and Critical Care Medicine. 2019 Dec15;200(12):1477-86




American Journal of Respiratory and Critical Care Medicine. 2019 Dec15;200(12):1477-86

# Safety and Adverse Events after Targeted Lung Denervation for Symptomatic Moderate to Severe Chronic Obstructive Pulmonary Disease (AIRFLOW)

- Randomized, sham- controlled, double-blind, prospective, multicenter study
- Study participants (n= 82), 41 in each arm
- Intervention : treatment arm received Nuvaira lung denervation therapy (Nuvaira )

American Journal of Respiratory and Critical Care Medicine. 2019 Dec15;200(12):1477-86

# Safety and Adverse Events after Targeted Lung Denervation for Symptomatic Moderate to Severe Chronic Obstructive Pulmonary Disease (AIRFLOW)

Total Predefined Primary Endpoint Respiratory Adverse Events 3–6.5 Months after Procedure

| Diagnosis (Patient Could Have Multiple Events) | Sham Group (*n* = 41) [% (*n*)] | TLD Group (*n* = 41) [% (*n*)] | *P* Value |
|---|---|---|---|
| Bronchitis, worsening | 4.9 (2) | — | 0.4938 |
| COPD exacerbation | 43.9 (18) | 26.8 (11) | 0.1731 |
| Discovered airway effects that require a therapeutic intervention | — | 2.4 (1)* | 1.0000 |
| Dyspnea, worsening | 22.0 (9) | 4.9 (2) | 0.0496 |
| Influenza | 2.4 (1) | — | 1.0000 |
| Pneumonia | 4.9 (2) | 2.4 (1) | 1.0000 |
| Respiratory infection | — | — | — |
| Respiratory failure | — | — | — |
| Tachypnea | — | — | — |
| Wheezing | 2.4 (1) | — | 1.0000 |
| Total | 70.7 (29) | 31.7 (13) | 0.0008 |

American Journal of Respiratory and Critical Care Medicine. 2019 Dec15;200(12):1477-86

# Safety and Adverse Events after Targeted Lung Denervation for Symptomatic Moderate to Severe Chronic Obstructive Pulmonary Disease (AIRFLOW)

Nonserious Respiratory Adverse Events 3–6.5 Months after Procedure

| Diagnosis (Patient Could Have Multiple Events) | Sham Group (*n* = 41) [% (*n*)] | TLD Group (*n* = 41) [% (*n*)] | *P* Value |
|---|---|---|---|
| Bronchitis, worsening | 4.9 (2) | — | 0.4938 |
| Common cold* | 4.9 (2) | 4.9 (2) | 1.0000 |
| Congestion | — | — | — |
| COPD exacerbation† | 36.6 (15) | 17.1 (7) | 0.0797 |
| Cough | 14.6 (6) | 2.4 (1) | 0.1088 |
| Dyspnea, worsening | 17.1 (7) | 4.9 (2) | 0.1549 |
| Hemoptysis | — | — | — |
| Hoarseness‡ | 4.9 (2) | 2.4 (1) | 1.0000 |
| Increased mucus§ | 2.4 (1) | 2.4 (1) | 1.0000 |
| Influenza | 2.4 (1) | — | 1.0000 |
| Mucosal candidiasis | — | — | — |
| Pneumonia | 2.4 (1) | — | 1.0000 |
| Pulmonary infection | — | — | — |
| Rhinitis/pollinosis | — | — | — |
| Sore throat‖ | — | 2.4 (1) | 1.0000 |
| Thoracic pain | — | — | — |
| Wheezing | 2.4 (1) | — | 1.0000 |
| Total | 65.9 (27) | 34.1 (14) | 0.0077 |

American Journal of Respiratory and Critical Care Medicine. 2019 Dec15;200(12):1477-86

# Secondary outcomes

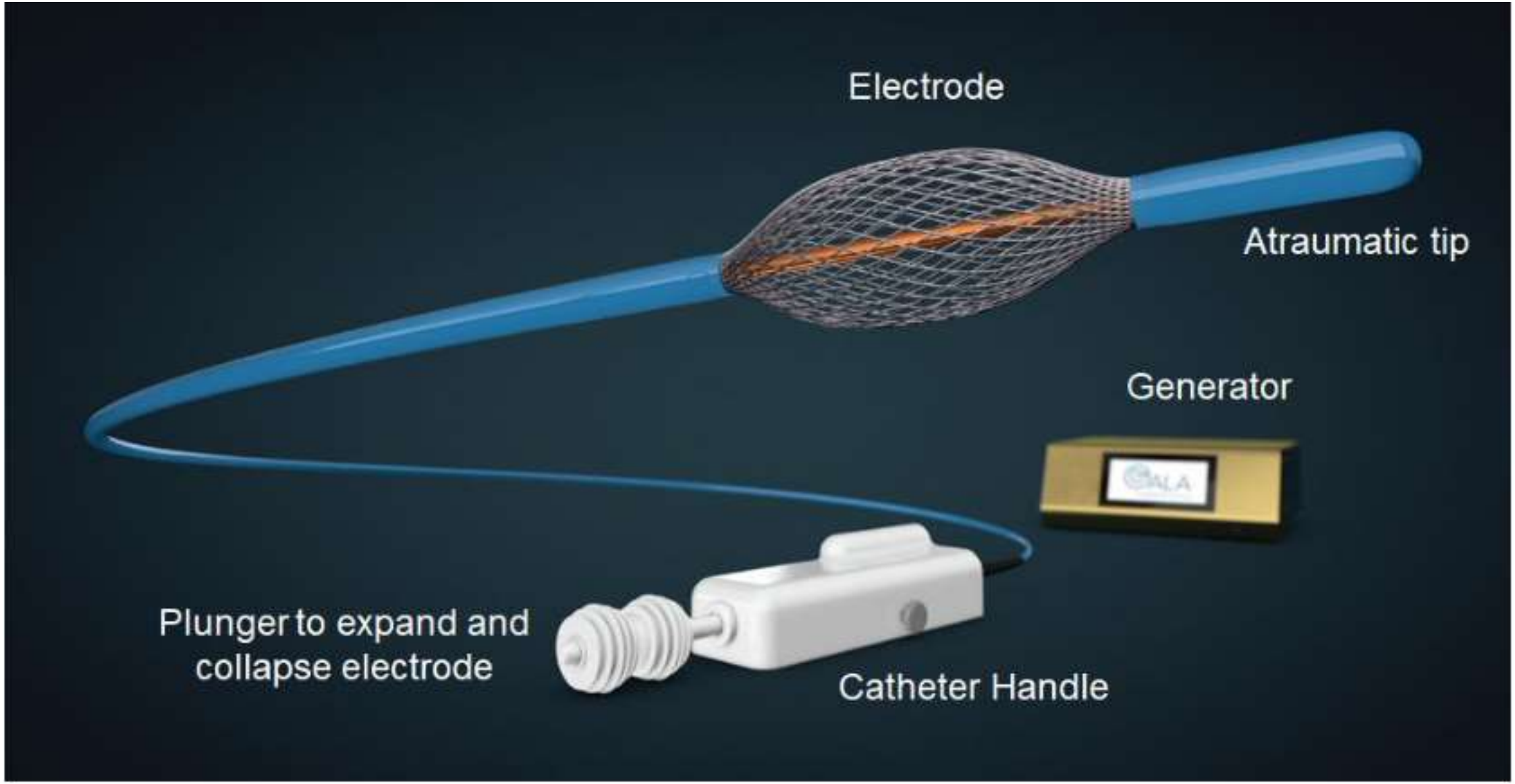
| Outcome | Sham Group (On Drug, Compared with Baseline Off Drug) (*n* = 41) [*Mean* ± *SD* (*n*)] | TLD Group (On Drug, Compared with Baseline Off Drug) (*n* = 41) [*Mean* ± *SD* (*n*)] | *P* Value for Sham vs. TLD (*t* Test) |
|---|---|---|---|
| $FEV_1$, ml | | | |
| 6 mo | 86.41 ± 179.5 (39) | 127.6 ± 201.0 (38) | 0.3453 |
| 12 mo | 103.5 ± 192.7 (37) | 74.32 ± 213.1 (37) | 0.5386 |
| FVC, ml | | | |
| 6 mo | 147.2 ± 360.8 (39) | 240.0 ± 389.7 (38) | 0.2815 |
| 12 mo | 211.4 ± 411.8 (37) | 235.4 ± 471.1 (37) | 0.8158 |
| RV, L | | | |
| 6 mo | −0.09 ± 0.9 (38) | −0.32 ± 0.8 (38) | 0.2431 |
| 12 mo | −0.23 ± 0.8 (37) | −0.35 ± 0.6 (37) | 0.4770 |
| SGRQ-C | | | |
| 6 mo | −3.76 ± 13.8 (39) | −8.31 ± 12.6 (37) | 0.1382 |
| 12 mo | −2.46 ± 14.5 (38) | −5.05 ± 14.4 (37) | 0.4414 |
| TDI | | | |
| 6 mo | −1.51 ± 3.7 (39) | 0.25 ± 3.2 (36) | 0.0318 |
| 12 mo | −1.24 ± 3.4 (38) | −1.17 ± 3.1 (36) | 0.9268 |
| CAT | | | |
| 6 mo | −3.18 ± 8.0 (39) | −1.97 ± 6.5 (38) | 0.4720 |
| 12 mo | −3.24 ± 8.3 (38) | −0.89 ± 6.4 (37) | 0.1754 |
| mMRC | | | |
| 6 mo | −0.26 ± 1.0 (39) | −0.47 ± 1.0 (38) | 0.3368 |
| 12 mo | −0.21 ± 1.0 (38) | −0.44 ± 0.8 (36) | 0.2790 |

American Journal of Respiratory and Critical Care Medicine. 2019 Dec15;200(12):1477-86

# Bronchial Rheoplasty

- RheOx® bronchial rheoplasty (Gala Therapeutics, San Carlos, CA, USA) delivers short bursts of high-frequency electrical energy to the airway epithelium and submucosal tissue layers in order to target goblet cells
- This causes cell death by disrupting cellular homeostasis  (osmotic swelling and apoptosis)
- Preserves  architectural function of the tissue, permitting subsequent regeneration of normalized epithelium and a reduction in airway mucus production.

Am J Respir Crit Care Med Vol 200, Iss 12, pp 1477–1486, Dec 15, 2019




Am J Respir Crit Care Med Vol 200, Iss 12, pp 1477–1486, Dec 15, 2019

- Treatment is delivered from second to seventh generation airways
- The procedure is performed in two separate treatments (one lung per treatment) with one month in between

Am J Respir Crit Care Med Vol 200, Iss 12, pp 1477–1486, Dec 15, 2019

# Bronchial Rheoplasty for Treatment of Chronic Bronchitis

## Twelve-Month Results from a Multicenter Clinical Trial

Arschang Valipour[1], Sebastian Fernandez-Bussy[2,3], Alvin J. Ing[4], Daniel P. Steinfort[5,6], Gregory I. Snell[7], Jonathan P. Williamson[4], Tajalli Saghaie[4], Louis B. Irving[5,6], Eli J. Dabscheck[7], William S. Krimsky[8,9], and Jonathan Waldstreicher[9]

- Two prospective, multicenter, single-arm clinical studies
- Study participants n=30 in each study
- Intervention :
- 1st session - Endobronchial biopsy from right bronchial airway followed by treatment of right lung
- 2nd session (1 month later) Endobronchial biopsy from left side followed by treatment of left lung
- 3rd session for bilateral airway biopsy - sample collection only, 3 months after the second treatment
- Primary outcome : No serious adverse events reported till 6 months

Am J Respir Crit Care Med Vol 200, Iss 12, pp 1477–1486, Dec 15, 2019

## Change from Baseline in Component Scores from CAT and SGRQ Questionnaires

| Measures(Mean ± SD ) | Baseline | 6 months | Change from baseline to 6 months | 12 months | Change from baseline to 12 months |
|---|---|---|---|---|---|
| CAT total score | 25.6 ± 7.1 | 17.7 ± 7.1 | −7.9 ± 8.3 | 18.8 ± 9.4 | −7.0 ± 8.9 |
| | | | | | |
| SGRQ total score | 59.6 ± 15.3 | 45.0 ± 20.0 | −14.6 ± 19.4 | 44.3 ± 21.9 | −15.2 ± 20.4 |

## Histopathology Results: Goblet Cell Hyperplasia Scores

| | Baseline | Follow up | Change from baseline |
|---|---|---|---|
| N (lungs biopsied) | 54 | 54 | |
| Mean score(SD) | 1.48 (0.91) | 0.91 (0.81) | -0.57* |
| 95% CI | 1.23 to 1.73 | 0.69 to 1.13 | -0.83 to -0.32 |

Am J Respir Crit Care Med Vol 200, Iss 12, pp 1477–1486, Dec 15, 2019

# Goblet Cell Hyperplasia Score: Change by Baseline Score

| Baseline goblet cell hyperplasia score N=54 Airway Biopsies | Improved | No change | worsened |
|---|---|---|---|
| 0 | 0 | 5 | 2 |
| 1 | 6 | 13 | 3 |
| 2 | 14 | 2 | 1 |
| 3 | 7 | 1 | 0 |

Am J Respir Crit Care Med Vol 200, Iss 12, pp 1477–1486, Dec 15, 2019

# Metered cryospray for patients with chronic bronchitis in COPD

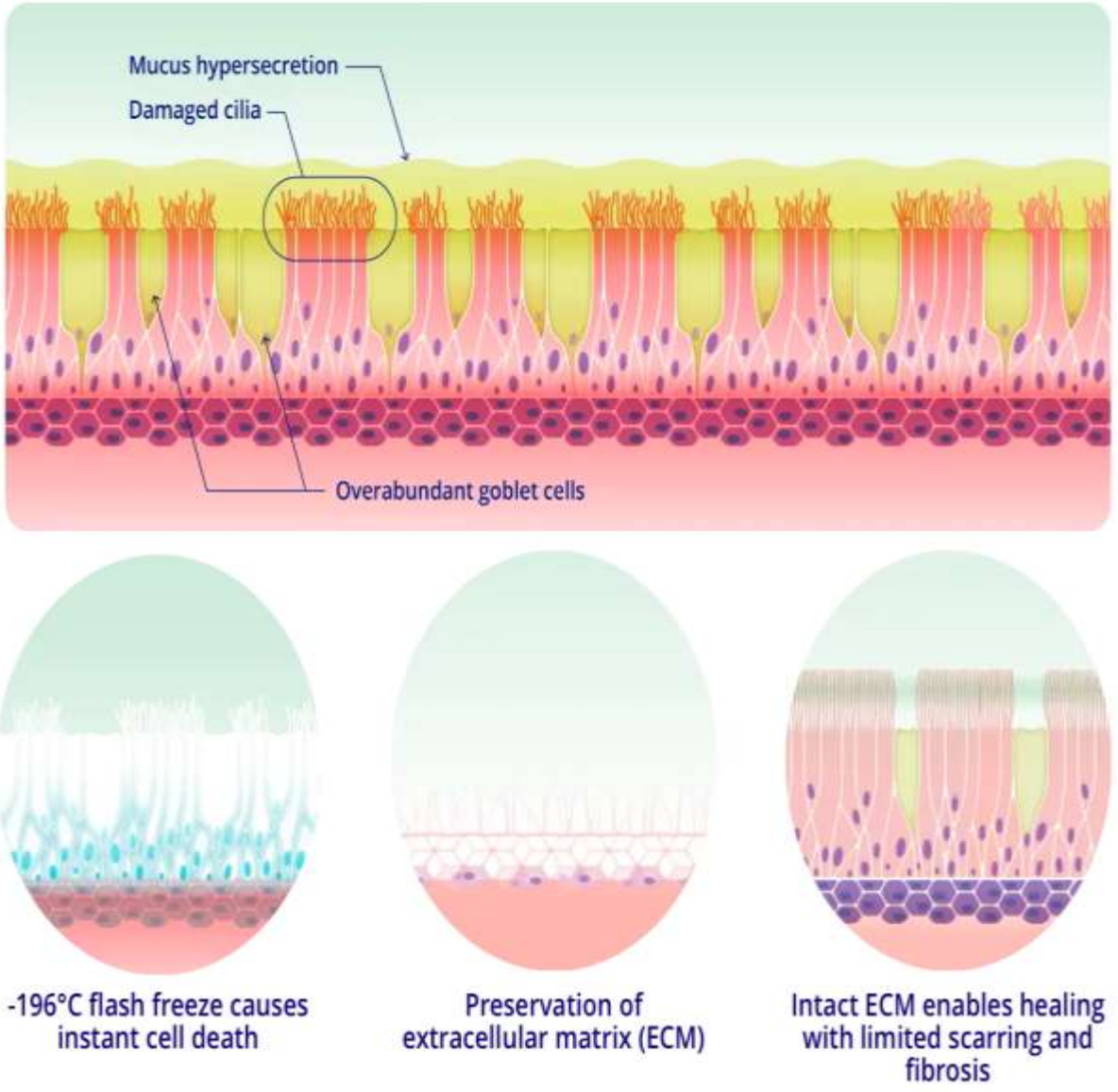
- Using a specially developed algorithm, programmed doses of liquid nitrogen are delivered in a radial spray, termed metered cryospray, to the bronchial airways.
- It is designed to cryoablate abnormal epithelium and excessive mucous-producing goblet cells to a depth of 0.1–0.5mm and a width up to 10mm
- Re-epithelialisation with healthy mucosa has been demonstrated within 48 h of cryospray treatment, and with durability to 106 days.

European Respiratory Journal. 2020 Dec 1;56(6)

# Metered cryospray for patients with chronic bronchitis in COPD

- Rejuven Air system (CSA Medical, Lexington, MA, USA) consists of a console which stores liquid nitrogen, and a disposable catheter with a radial spray head inserted through the working channel of a flexible bronchoscope

European Respiratory Journal. 2020 Dec 1;56(6)




European Respiratory Journal. 2020 Dec 1;56(6)

# A prospective safety and feasibility study of metered cryospray for patients with chronic bronchitis in COPD

- Prospective, open-label, single-arm study
- Study subjects (n=35)
- First treatment delivered metred cryospray to the right lower lobe and main stem bronchus, the second to the left lower lobe and main stem bronchus, and the third to both upper lobes, any residual main stem bronchus and the distal end of the trachea
- Gap 30–45 days in between each session

European Respiratory Journal. 2020 Dec 1;56(6)

# A prospective safety and feasibility study of metered cryospray for patients with chronic bronchitis in COPD

- Primary end-point, the mean change in total SGRQ score (ΔSGRQ total) from baseline to 3 months

−6.4 (95% CI −11.4 to −1.3; p=0.01)

- 12-month follow-up period, FEV1 declined to  −96.5 mL (95% CI −169.0 to −23.9; p=0.01).
- The mean change in 6-min walk distance at 9 months, 24.3 m (95% CI −0.4 to 49.0 m; p=0.05)

European Respiratory Journal. 2020 Dec 1;56(6)

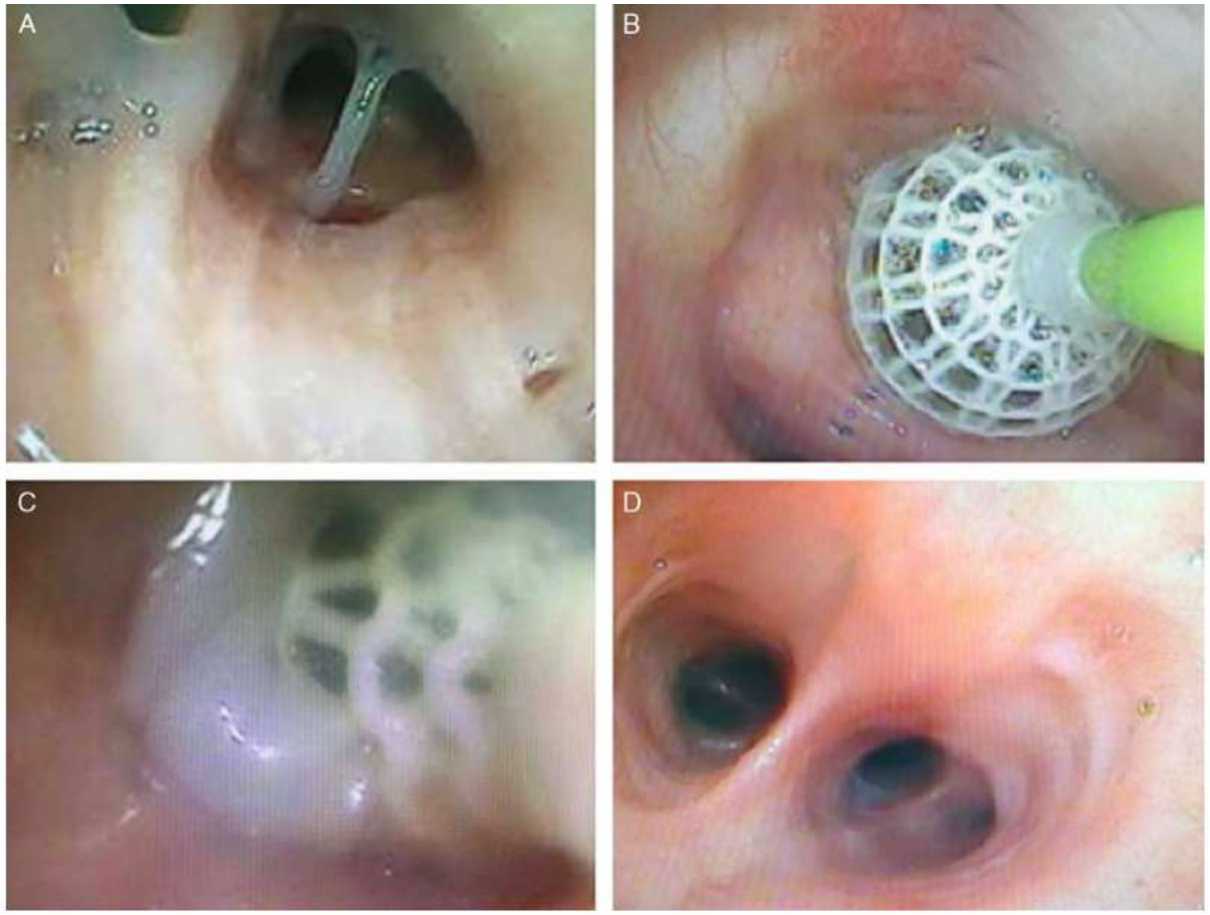
# Resector Balloon Desobstruction

- In this technique, the balloon insertion  is done into the bronchial lumen till the mucosal

obstruction covers the balloon

- The balloon is repeatedly inflated and deflated until lumen patency is established
- Balloon operated by electronic pump in a regular pulse mode and the force applied directly to the bronchial mucosa with of 2.2 to 2.5 bar compressing the hyperplasic goblet cells

Journal of Bronchology & Interventional Pulmonology. 2015 Jul 1;22(3):209-14




Journal of Bronchology & Interventional Pulmonology. 2015 Jul 1;22(3):209-14

# Use of Resector Balloon Desobstruction in Patients With Severe Chronic Obstructive Pulmonary Disease

- Pilot study
- Study participants (n= 10)
- Intervention – Balloon deobstruction
- Average duration = 60min

Journal of Bronchology & Interventional Pulmonology. 2015 Jul 1;22(3):209-14

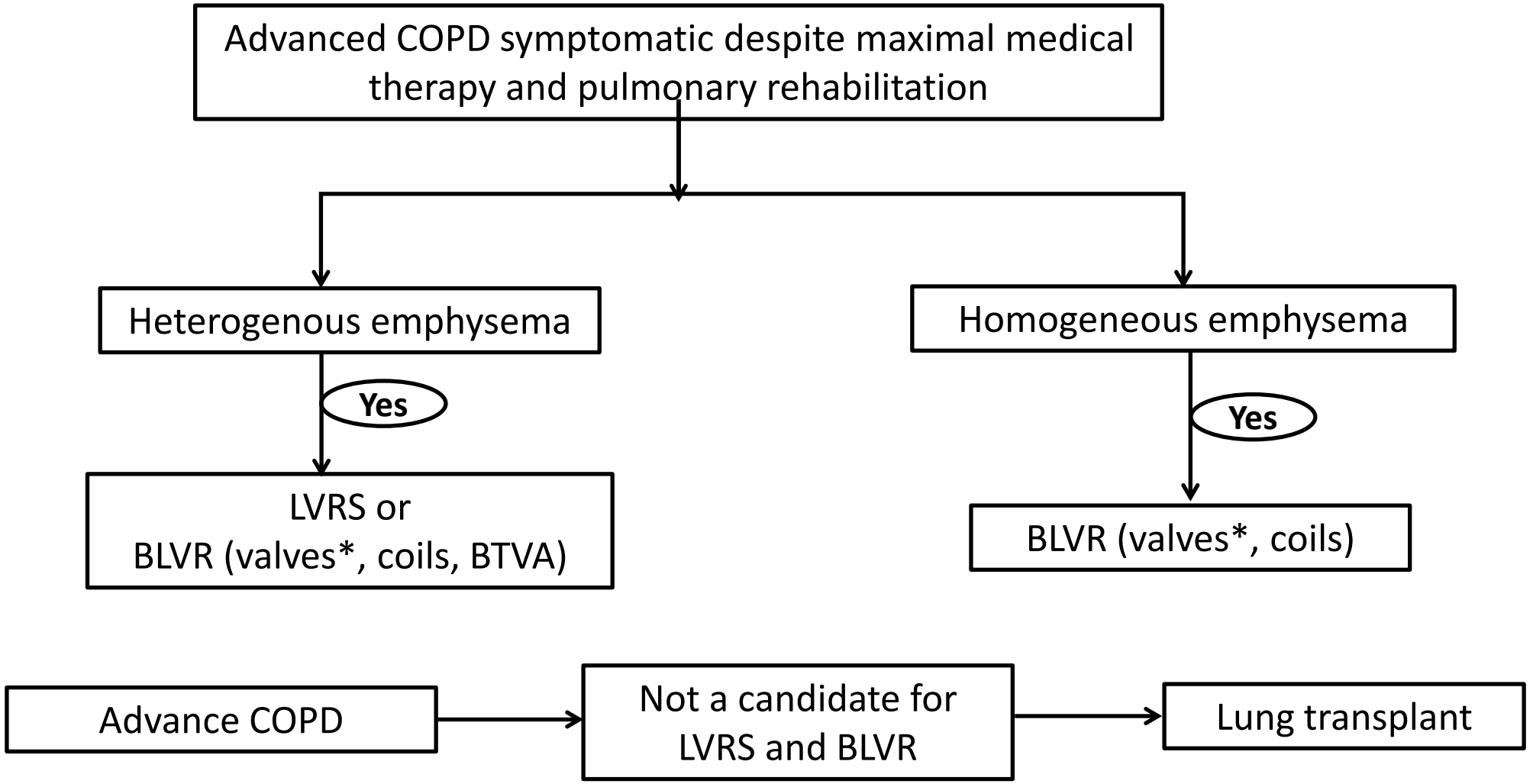
| $FEV_1$ (L) | | | Modified Borg Dyspnea Scale | | | Resting Oxygen Saturation (%) | | |
|---|---|---|---|---|---|---|---|---|
| | After | | | After | | | After | |
| Before | 1 wk | 1 mo | Before | 1 wk | 1 mo | Before | 1 wk | 1 mo |
| 0.69 | 1.19 | 1.52 | 9 | 3 | 3 | 85 | 93 | 94 |
| 1.17 | 1.33 | 1.31 | 7 | 3 | 3 | 90 | 95 | 94 |
| 0.55 | 0.61 | 0.78 | 10 | 7 | 7 | 82 | 90 | 91 |
| 0.71 | 0.74 | 1.06 | 10 | 3 | 3 | 89 | 95 | 97 |
| 0.99 | 1.06 | 1.21 | 7 | 4 | 3 | 89 | 96 | 95 |
| 1.16 | 1.41 | 1.59 | 7 | 3 | 3 | 91 | 96 | 96 |
| 0.98 | 1.19 | 1.21 | 9 | 9 | 9 | 88 | 92 | 91 |
| 0.91 | 1.06 | 1.05 | 10 | 3 | 3 | 87 | 93 | 93 |
| 0.99 | 1.00 | 1.37 | 7 | 3 | 3 | 88 | 94 | 93 |
| 0.70 | 1.06 | 1.00 | 10 | 3 | 3 | 88 | 94 | 96 |

Journal of Bronchology & Interventional Pulmonology. 2015 Jul 1;22(3):209-14

# FDA approved devices

- Zephyr valves endobronchial valves (Pulmonx)
- Spiration valve system (Olympus)

# Summary:




***BLVR using valves should be limited to subjects without evidence of collateral ventilation**
**BLVR: bronchoscopic lung volume reduction, BTVA: bronchoscopic thermal vapor ablation, LVRS: lung volume reduction surgery**