University of Pittsburgh

2019 Update in Pulmonary Medicine

Niall Prendergast

COPD

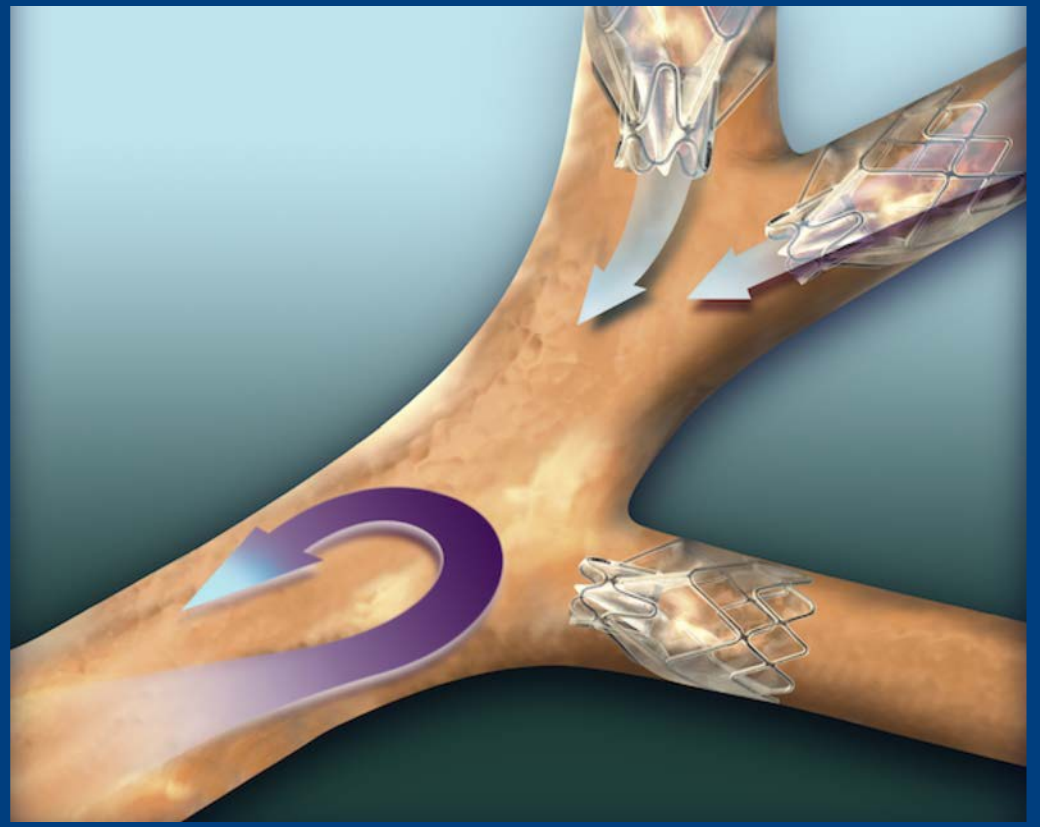
- Prevalent and morbid
  - Over 12 million American adults diagnosed as of 2016
  - Estimated $49 billion in health care costs in 2020
  - Fourth-leading cause of death in US
- Mainstays of therapy
  - Smoking cessation, oxygen, vaccinations
  - Pulmonary rehab
  - Inhaled bronchodilators
- Advanced options include LVRS and lung transplantation

New Therapies

- Bronchoscopic Lung Volume Reduction
- Bronchial Rheoplasty
- Targeted Lung Denervation

Endobronchial Valves - Theory

- Valves induce lobar atelectasis
- Hyperinflation improves
  - Respiratory muscles work falls
- Less-diseased lung expands
  - V/Q matching improves



https://upload.wikimedia.org/wikipedia/commons/2/22/Endobronchial_valves_placed_in_airways.png

Endobronchial Valves - Data

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

* For between-group mean differences, 95% confidence intervals and P values were calculated with the use of a two-sided t-test. For between-group median differences, values ware calculated with the use of a Hodges–Lehmann estimator with nonparametric 95% confidence intervals, and P values by means of a two-sided Wilcoxon rank-sum test.
† Values in this category were calculated in nonparametric analyses, so the imputed median shift is not the simple difference between the treatment group and the control group.
‡ Scores on the St. George's Respiratory Questionnaire (SGRQ) range from 0 to 100, with higher scores indicating a worse quality of life. The minimal clinically important difference is 4 points.
§ Scores on the Modified Medical Research Council dyspnea scale range from 0 to 4, with higher scores indicating a greater severity of dyspnea. The minimal clinically important difference is 1 point.

- Lung function and exercise tolerance are best-studied
- Breathlessness a common secondary endpoint
- Effects greatest in those without collateral ventilation
- Mortality not assessed

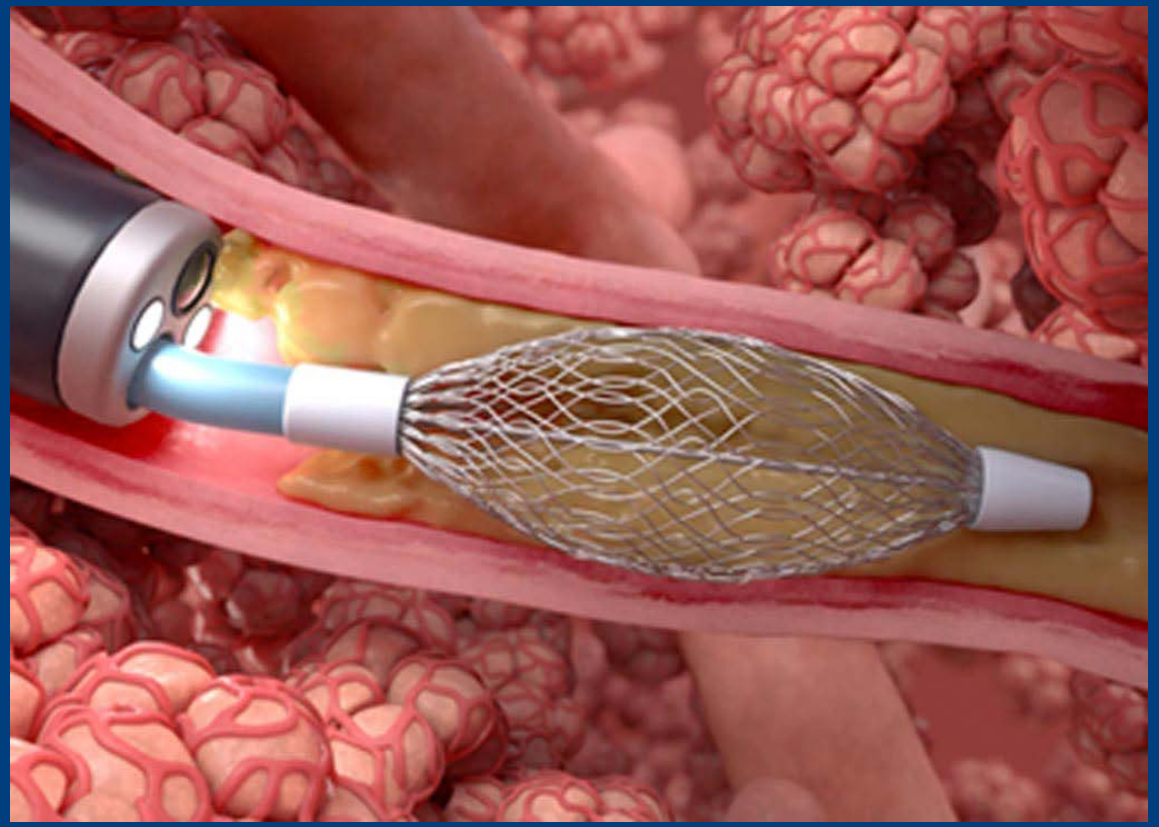
Sciurba et al, NEJM 2010

Endobronchial Valves - Practice

Trial Inclusion Requirements	Current Pitt Practice
• Heterogeneous emphysema	• Complete fissures on CT, Chartis
• FEV1 15-45% predicted	• Severe obstruction (<~50%)
• Residual volume >150%	• RV >175%
• $PaCO_2 < 50$, $PaO_2 > 45$ on RA	• Generally, similar
• Not A1AT-deficient	• Same
• No other contraindications	• Same

Rheoplasty - Theory

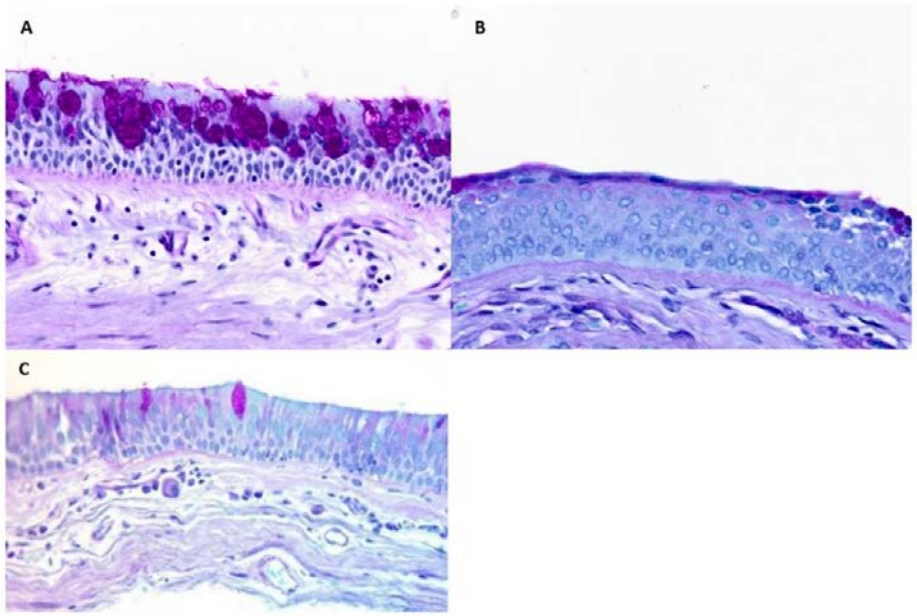
- Chronic bronchitis is related to goblet-cell-rich airway metaplasia
- High-frequency electrical energy kills airway epithelium
- Airways regenerate without preexisting metaplasia



https://www.hospimedica.com/surgical-techniques/articles/294775783/rheoplasty-system-targets-bronchitis-mucus-plugging.html

Rheoplasty - Data

Figure 1: Endobronchial histology from a patient treated with Bronchial Rheoplasty



Legend: PAS stained section of the right bronchus intermedius of subject 001-002. The goblet cells are typified by the magenta cytoplasmic vacuoles seen in the most superficial epithelial layer. On Day 0 immediately before therapy (Panel A) significant goblet cell hyperplasia can be seen (semi-quantitative assessment score of 2). At 30 days (Panel B), the epithelium demonstrates squamous metaplasia, indicating a regenerative process. Right bronchus intermedius at 120 days after the initial treatment (Panel C), demonstrating complete regeneration of pseudostratified columnar epithelium with a resolution of goblet cell hyperplasia (semi-quantitative assessment score of 0)

- Goblet cell hyperplasia reduced
- Dyspnea symptoms improved
- Significant rate of exacerbations
- US trial ongoing

Valipour et al, ERJ 2018

University of Pittsburgh

Gala Early Feasibility Study of RheOx (Gala_EFS)
ClinicalTrials.gov Identifier: NCT03631472

Recruitment Status : Recruiting
First Posted : August 15, 2018
Last Update Posted : February 19, 2019

Rheoplasty - Practice

Inclusion

- Chronic bronchitis for at least 2yrs
- Moderate to severe obstruction
- At least one exacerbation last year
- At least 10 pack-year history

Exclusion

- Current or recent infection
- >10mg prednisone daily
- Smoking in last six months
- Other serious medical problems

Denervation - Theory

- Parasympathetic airway nerves mediate smooth muscle tone, mucus secretion, and airway reactivity
- Anticholinergic inhalers target this pathway
- What if there were a… permanent solution?

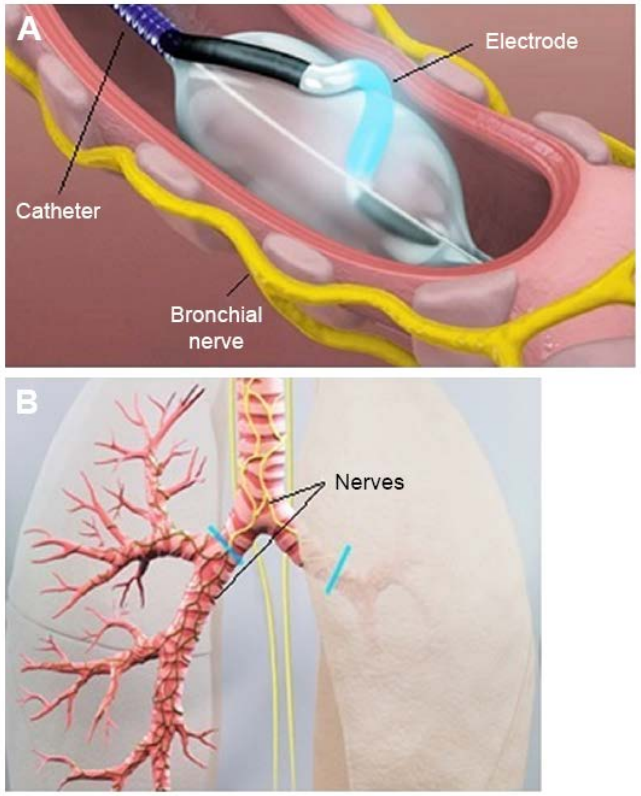


Figure 2 Representative ablation procedure.
Notes: (**A**) Image of a representative ablation. The catheter is in left bronchus with electrode in the lateral position. Catheter is rotationally repositioned to achieve complete circumferential treatment. Both the catheter and electrode are filled with cooled fluid to protect the airway inner surface during ablation. (**B**) Blue lines designate the area of circumferential ablation in main bronchi. Attenuation of nerve fibers along the outside of the airway is represented by change in color.

Valipour et al, Int J COPD 2018

Denervation - Data

Table 2A. Total Pre-Defined Primary Endpoint Respiratory Adverse Events 3 to 6.5 Months Post-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**

- Lower “adverse respiratory events,” driven primarily by COPD exacerbations and dyspnea
- Safety events were not statistically significantly different
- Effect on lung function likely similar to LAMA monotherapy

Slebos et al, AJRCCM in press

Denervation - Practice

Inclusion

- FEV1 30-60% predicted
- At least 10 pack-year history, but not a current smoker
- At least 2 moderate or 1 severe exacerbation in previous year

Exclusion

- BMI <18 or >35
- >3 respiratory hospitalizations in previous year
- Non-COPD lung disease
- Prednisone >10mg daily
- Other significant medical problems

Take-Home Points

- BLVR appropriate for classic emphysema phenotype
- TLD and rheoplasty appropriate for chronic bronchitis phenotype
- Optimal medical therapy, pulmonary rehab likely to remain backbone of COPD care