COPD School 2021

Session Ⅱ. Update of the Non-pharmacological Management of COPD

Bronchoscopic Intervention for COPD

2021.05.29

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정병호

Other than LVR

Bronchial rheoplasty for chronic bronchits (AJRCCM 2020)

Targeted lung denervation, AIRFLOW-2 (AJRCCM 2019)

Airway bypass track stent

Clinical pilot study (Ann Thorac Surg 2003)

EASE (Lancet 2011) : no sustained long-term effects

BioLVR

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ASPIRE (ERJ 2015) : Effective, but terminated prematurely for business-related reasons

1959 2003 2007 2008 2009 2010 2011 2012 2013 2015 2016 2017 2018 2019 2020

Surgical approach to pulmonary emphysema

NETT (National Emphysema Treatment Trial, NEJM 2003)

2008 FDA approval for post-Op persistent air leak

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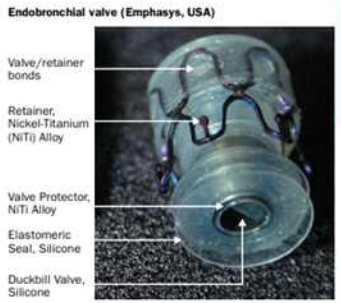

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Incomplete occlusion of the upper lobes (JTCVS 2007)

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REACH (Respiration 2019)
: heterogeous emphysema, lobar treatment, similar effect and complications

LVRCs

Clinical pilot study (Ther Adv Respir Dis 2010)

RENEW (JAMA 2016) : both upper lobes, regardless of CV

TVA

Clinical pilot study (Ann Thorac Surg 2009)

STEP-UP (Lancet Respir Med 2016)
: Subsegments can be targeted
: Pneumonitis

Rationale for lung volume reduction

- Lung hyperinflation: major contributor to poor respiratory function
  - ↑ sensation of dyspnea
  - ↓ exercise capacity (← distortions of the chest wall and pulmonary muscle mechanics)
  - ↓ cardiac function
  - ↑ mortality

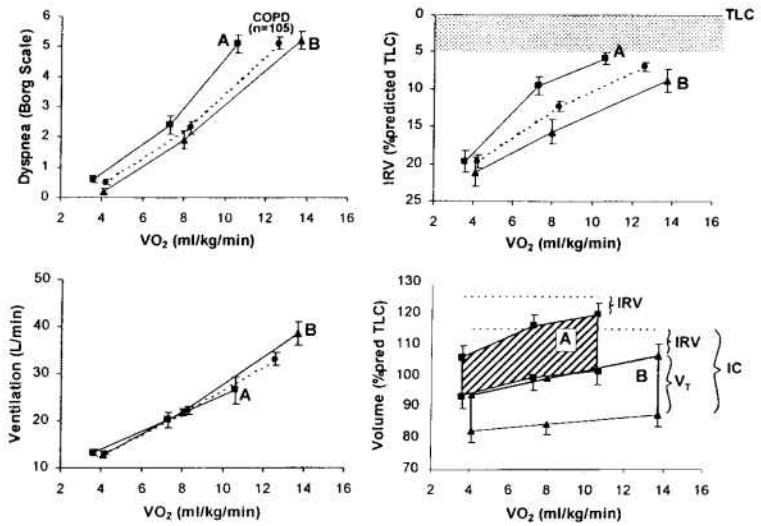


Figure 4. Ventilatory responses to exercise are shown in COPD (n = 105) and its subgroups: *A* with a low D_{LCO} < 50% predicted (n = 24), and *B* with a better preserved D_{LCO} > 50% predicted (n = 24). Group A had significantly ($p < 0.05$) greater exertional dyspnea, greater levels of lung hyperinflation, and earlier attainment of a limiting mechanical restriction (i.e., minimal IRV, *shaded area*) than Group B.

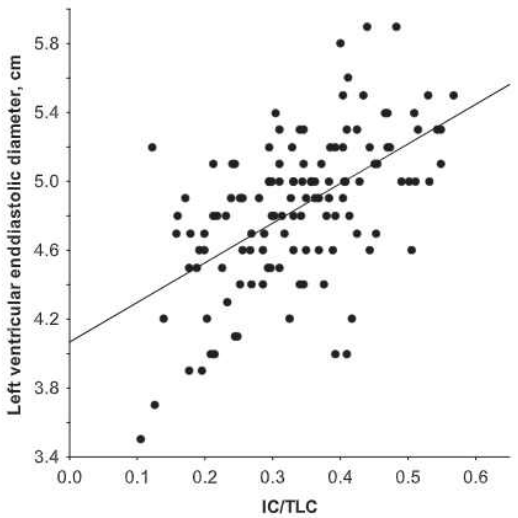


FIGURE 1. Correlations between IC/TLC and left ventricular end-diastolic diameter ($r = 0.56$; $P < .001$; n = 125). IC/TLC = inspiratory-to-total lung capacity ratio.

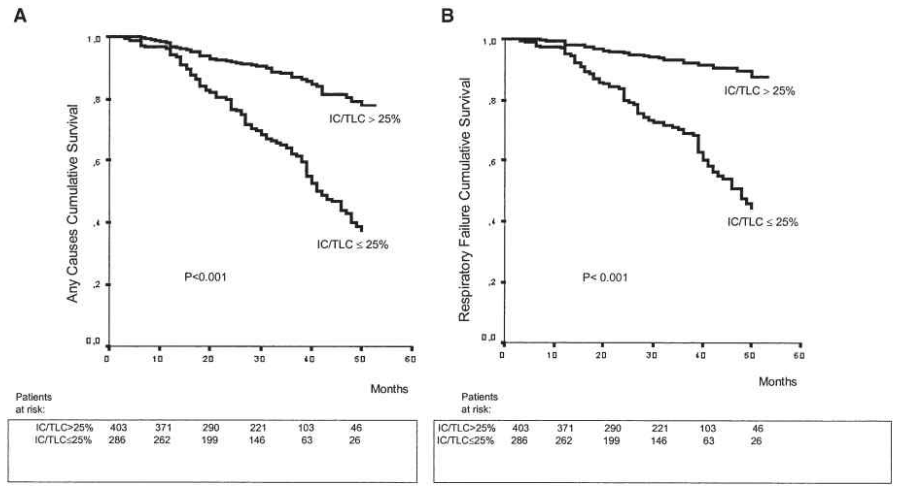


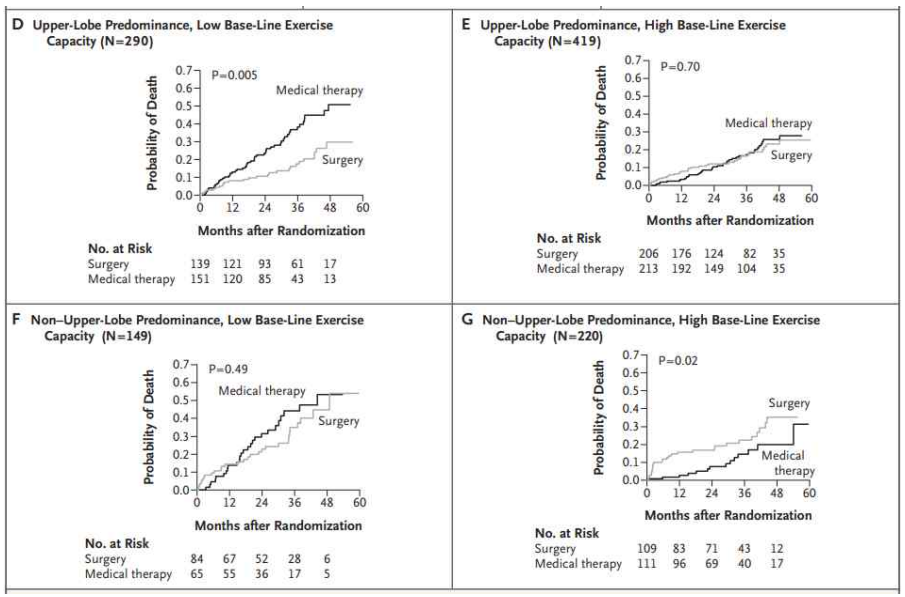
Figure 2. Static lung hyperinflation measured by the IC/TLC ratio, using a 25% value as threshold. Kaplan–Meier curves for all causes and respiratory failure cause are shown. Survival differed significantly among both groups ($p < 0.001$ by the log-rank test) as seen in (*A*) and (*B*).

Casanova C et al. Am J Respir Crit Care Med 2005;171(6):591–7.
O'Donnell DE et al. Am J Respir Crit Care Med 2001;164(5):770–7.
Watz H et al. Chest 2010;138(1):32–8.

History of LVRS

- Brantigan OC et al. A surgical approach to pulmonary emphysema. Am Rev Respir Dis 1959;80:194–206.
  – "*an operation directed at restoration of a physiologic principle … not concerned with the removal of pathologic tissue.*"
- Two case series (20 and 150 pts) preceded the RCTs in LVRS (published in 1999 ~).

- National Emphysema Treatment Trial (NETT): 1200 pts



	Mortality	Exercise capacity/ Symptoms
Upper lobe predominant emphysema, low exercise	Improved	Improved
Upper lobe predominant emphysema, high exercise	No change	Improved
Non-upper lobe predominant emphysema, low exercise	No change	No change
Non-upper lobe predominant emphysema, high exercise	Worsened	No change

Fishman A et al. N Engl J Med 2003;348(21):2059–73.

Current state of LVRS

- In USA from 2000–2010, only 3300 times of LVRS were performed.
  - Emergence of less invasive bronchoscopic LVR
  - Risk of perioperative morbidity and mortality
  - LVRS may preclude patients from undergoing lung transplantation (↑ postoperative bleeding, renal injury)

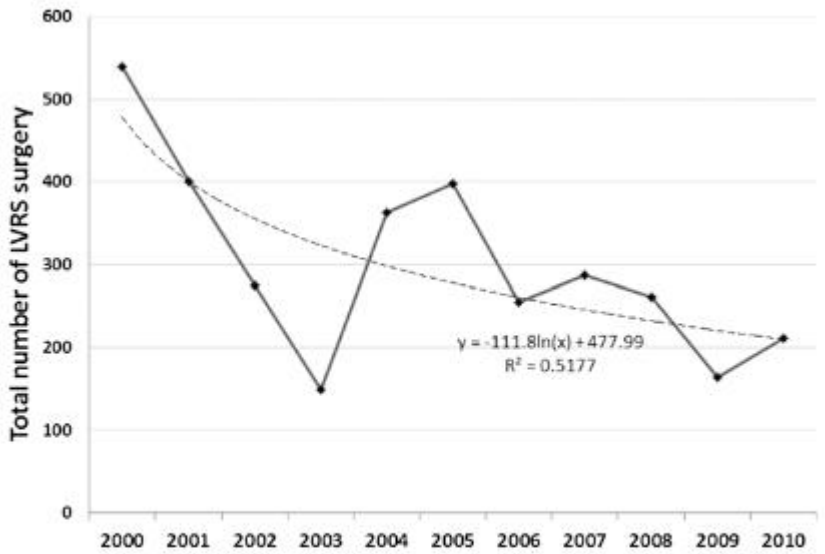


Figure 1 – *Trends in LVRS in the United States from 2000 to 2010. Dotted line represents best fit. LVRS = lung volume reduction surgery.*

Ahmad S et al. Chest 2014;146(6):e228–9.
Shigemura N et al. Transplantation 2013;96(4):421–5.

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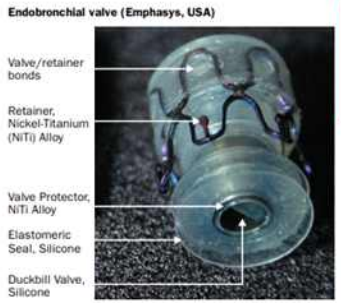

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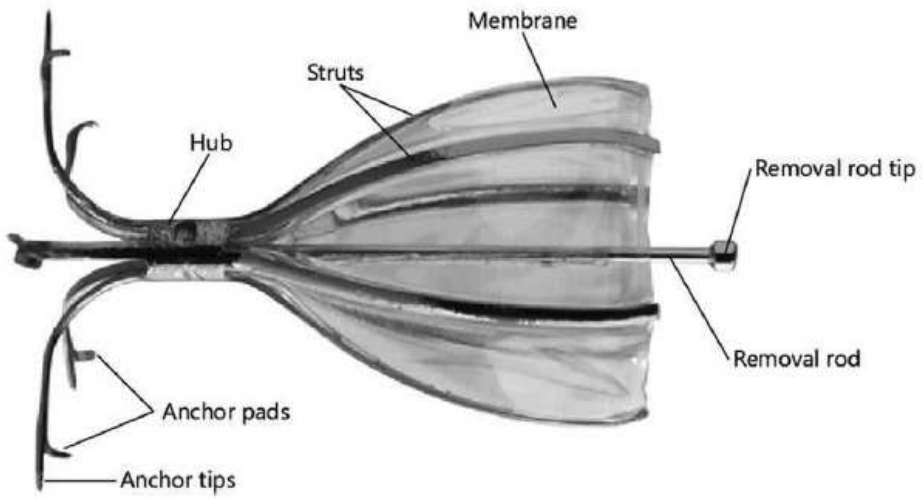
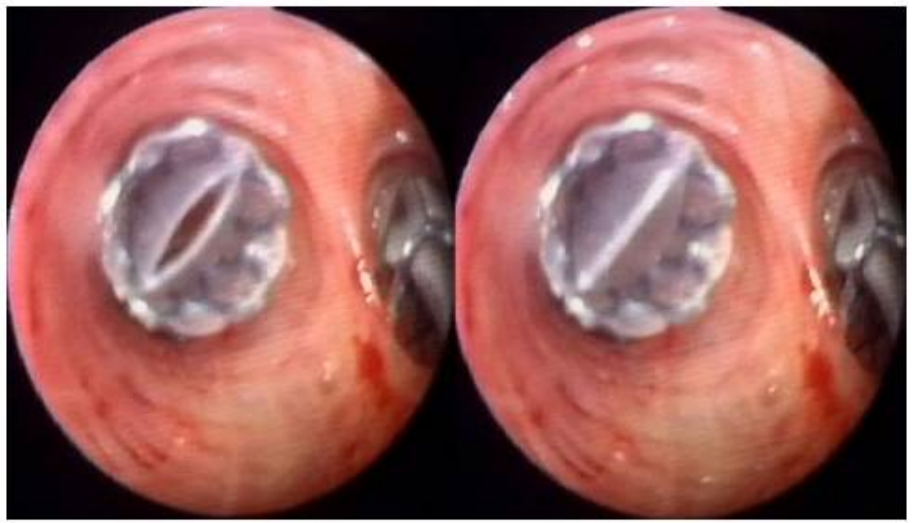
Roles of EBVs

- Block inspiration, permit exhalation and secretion
- EBVs are placed in the most air trapped lobe owing to emphysematous destruction
- Optimal valve placement results in lobar atelectasis and a significant reduction in end-expiratory lung volumes





VENT: the first RCT (Zephyr), in the USA

- The Endobronchial Valve for Emphysema Palliation Trial

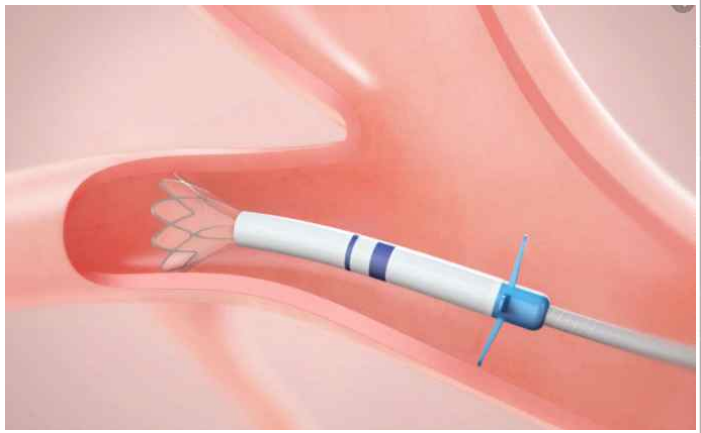


Table 2. Primary and Secondary Efficacy Outcomes in the Intention-to-Treat Population (Change from Baseline at 6 Months)*

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

Modest effect

Sciurba FC et al. N Engl J Med 2010;363(13):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

Predictive factors of improvements in the primary end points (FEV_1, 6MWT)

- Heterogeneity of emphysema between lobes in treated lung (> 15%)
- Presence of complete fissures (> 90%)

EUROVENT (European Vent Study - Herth FJ et al. Eur Respir J 2012;39(6):1334–42.)

- Similar results – modest effect
- Pts with complete fissures had better results with improvements in FEV_1 (16% *vs*. 2%)

Sciurba FC et al. N Engl J Med 2010;363(13):1233–44.

Intact fissures or not

- ↓ fissure integrity (FI) = incomplete fissure = collateral ventilation (CV) (+) = poor outcome
- Assessment tools for FI
  - Chartis system (Pulmonx Inc.): Balloon occlusion of the airway and monitoring flow
  - Quantitative HRCT (QCT) analysis of FI: “FI > 90%” = complete fissure = acceptable parameter to proceed with EBV insertion
- Neither technique is perfect

Table 3. Comparison of Patient Selection Methods for Endobronchial Valve Lung Volume Reduction Treatment

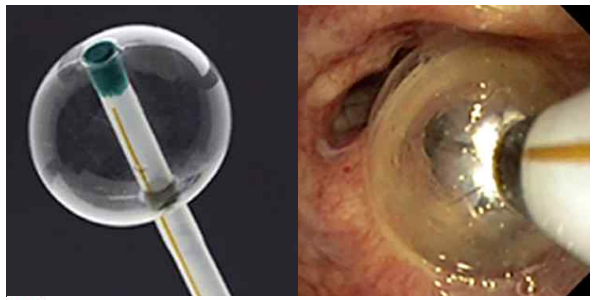
Subject Selection Method	Patients Recommended for Treatment (%)	Responder Rate (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
Chartis	54.5 (18/33)	77.8 (14/18)	**75.8 (25/33)**	77.8 (14/18)	73.3 (11/15)
QCT-Bayes	63.6 (21/33)	76.2 (16/21)	**78.8 (26/33)**	88.9 (16/18)	66.7 (10/15)
QCT, FI ⩾ 90%	60.6 (20/33)	75.0 (15/20)	75.8 (25/33)	83.3 (15/18)	66.7 (10/15)

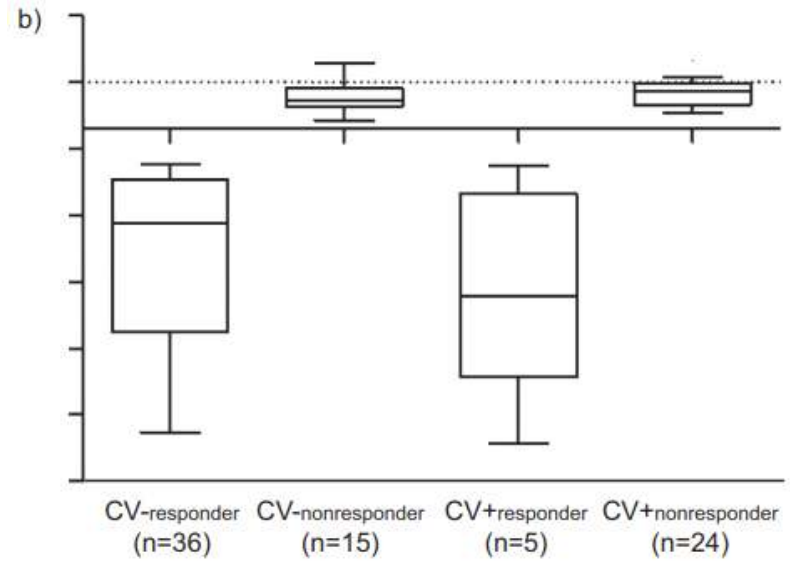
Definition of abbreviations: FI = fissure integrity; QCT = quantitative computed tomography.
Statistical differences in sensitivity and specificity between the different methods were evaluated using the Fisher exact test and were corrected for multiple comparisons. The analysis showed no statistical differences between Chartis and CT-based approaches in terms of sensitivity and specificity ($P > 0.55$).
Highlighted in bold are the differing accuracies between Chartis and QCT.

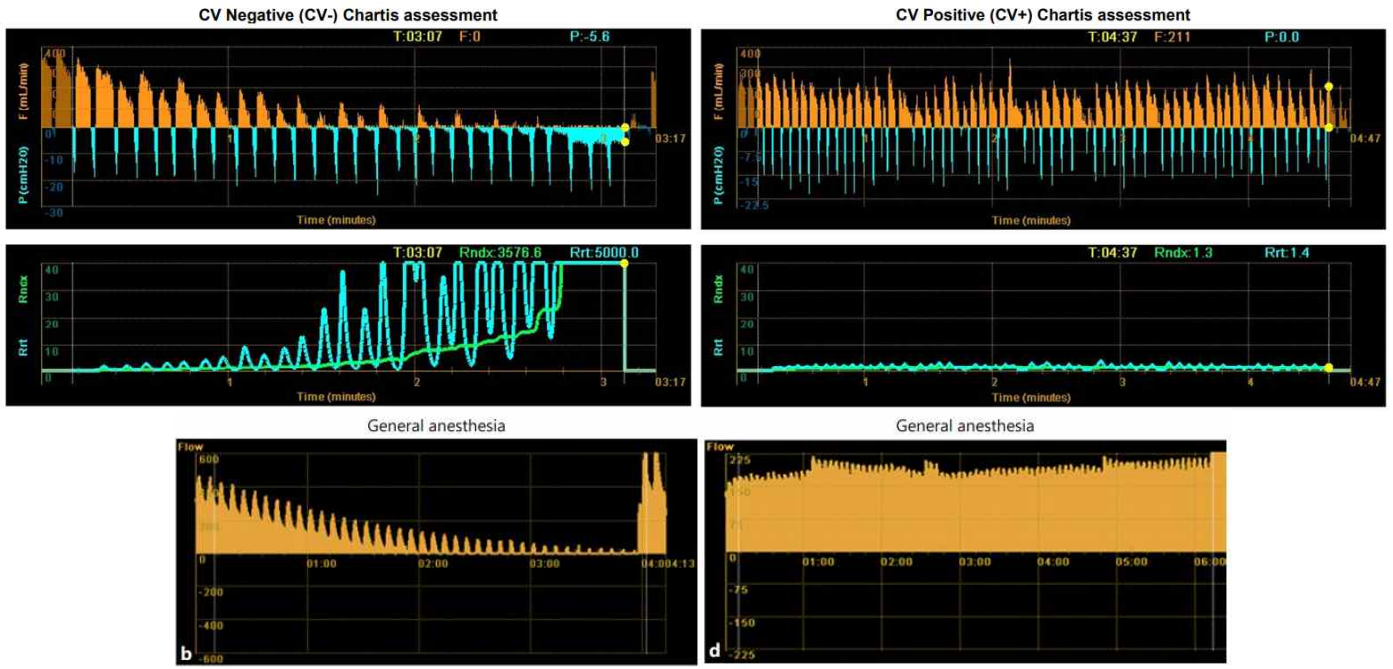
Schuhmann M et al. Am J Respir Crit Care Med 2015;191(7):767–74.

The Chartis-EBV trial

- Resistance value >10 → “CV Negative”, good candidate
- Resistance value <10 → “CV Positive”, no good candidate







Welling JBA et al. Respiration 2018;96:480–487.
Herth FJ et al. Eur Respir J 2013;41:302-308.

RCTs investigating Zephyr in severe emphysema with CV (–) using Chartis system

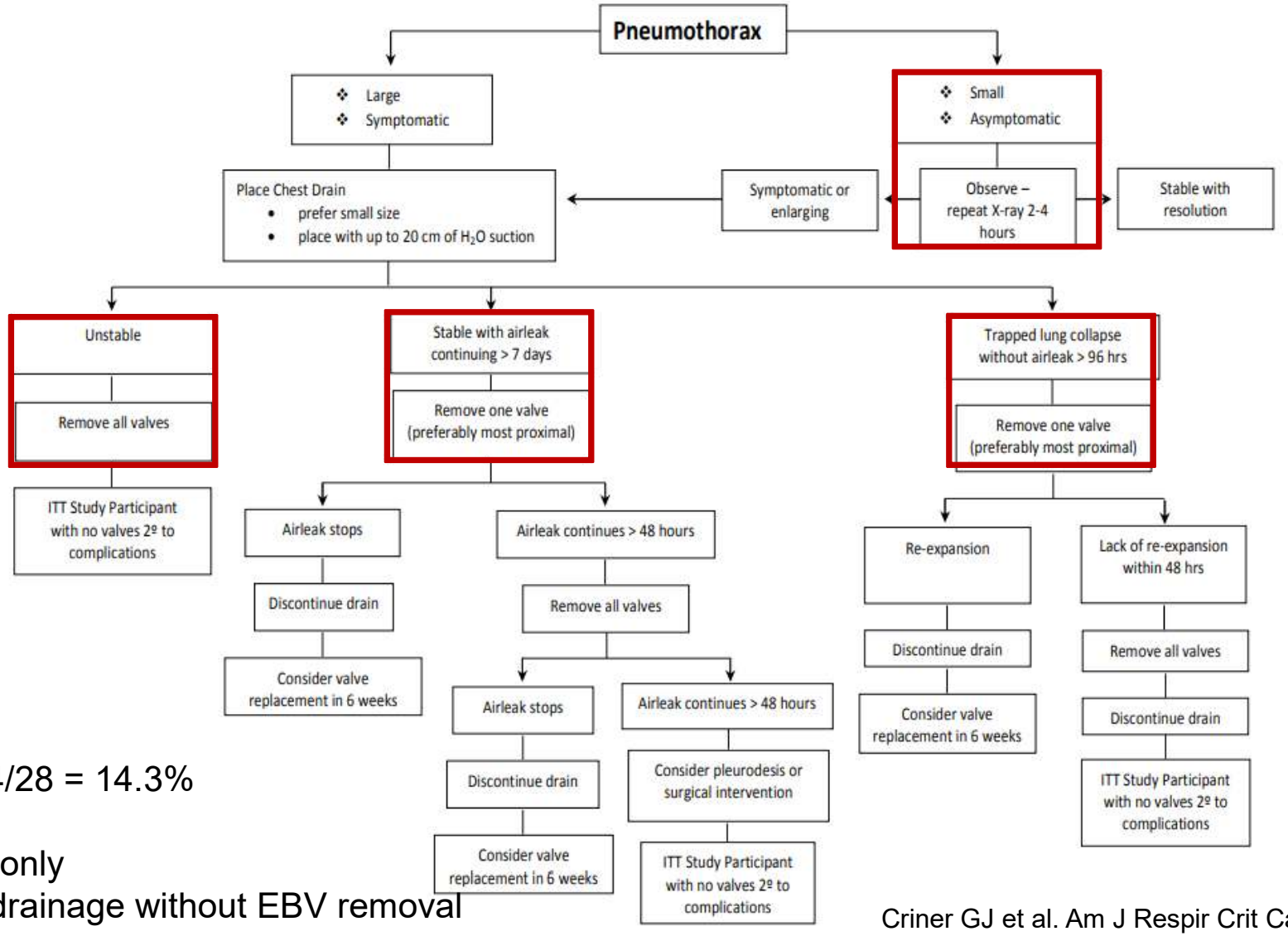
	STELVIO 2015	IMPACT 2016	TRANSFORM 2017	LIBERATE 2018
Patients, EBV / SoC	34 / 34	43 / 50	65 / 32	128 / 62
Age	58 ± 10	64 ± 6	65 ± 8	64 ± 7
FEV_1, % pred	29 ± 7	28 ± 6	30 ± 9	28 ± 7
RV, % pred	216 ± 36	277 ± 55	249 ± 52	225 ± 42
TLC, % pred	130 ± 13	145 ± 21	139 ± 19	134 ± 21
DLCO, % pred	38.7 ± 9.1	-	-	34.6 ± 11.3
6MWD, m	372 ± 90	308 ± 91	282 ± 94	311 ± 81
Homogeneity	Both	Homogeneous	Heterogeneous	Heterogeneous
Follow-up, month	6	3	6	12
Target-lobe volume reduction, ml	-1366	-1195	-1090	-1142
Outcome (ΔEBV-SoC)				
FEV_1, %	+18 (8–28)	+17 (8–26)	+29 (18–40)	+18 (10–26)
RV, ml	-831 (-1101 to -560)	-480 (-840 to -110)	-670 (-1090 to -250)	-522 (-770 to -270)
6MWD, m	+74 (47–100)	+40 (15–65)	+79 (46–111)	+39 (15–64)
SGRQ	-14.7 (-21.8 to -7.6)	-9.6 (-14.1 to -5.2)	-6.5 (-12.4 to -0.6)	-7.1 (-11.8 to -2.3)

STELVIO → Klooster K et al. N Engl J Med. 2015;373(24):2325-2335.
IMPACT→ Valipour A et al. Am J Respir Crit Care Med. 2016;194(9):1073-1082.
TRANSFORM → Kemp SV et al. Am J Respir Crit Care Med. 2017;196(12):1535-1543.
LIBERATE → Criner GJ et al. Am J Respir Crit Care Med. 2018;198(9):1151-1164.

Complications

	STELVIO 2015	IMPACT 2016	TRANSFORM 2017	LIBERATE 2018
Patients, EBV / SoC	34 / 34	43 / 50	65 / 32	128 / 62
Follow-up, months	6	3	6	12
Pneumothorax	18% vs 0% (p = 0.02)	26% vs 0% (p < 0.001)	23% vs 0% (p < 0.05)	33% vs 0% (p < 0.05)
COPD AE	12% vs 6% (p = 0.67)	16% vs 12%	11% vs 11%	30% vs 35%
Pneumonia	6% vs 3% (p = 0.67)	0% vs 2%	11% vs 3%	6% vs 8%
EBV-related events				
EBV migration	2 (6%)	2 (5%)	1 (2%)	3/501 (0.6%)
EBV expectoration	0	1 (2%)	2 (3%)	2/501 (0.4%)
Granulation tissue formation	1 (3%)	2 (5%)	-	-
Bronchial torsion	2 (6%)	-	-	-
Death	1 d/t end-stage COPD	1 in SoC (d/t pneumonia)	1 d/t pneumothorax	3 d/t pneumothorax 1 d/t respiratory failure

Protocol for pneumothorax management



Pneumothorax in SMC: 4/28 = 14.3%
(POD 0d, 4d, 3mo, 4mo)
- 2 patients: O2 therapy only
- 2 patients: chest tube drainage without EBV removal

Criner GJ et al. Am J Respir Crit Care Med. 2018;198(9):1151-1164.

Spiration Valve System (SVS) = (Intrabronchial valve, IBV)
(The EMPROVE and REACH trials)

- The main cause of failure in earlier studies
  - Per protocol, one segment or sub-segment of the RUL and the lingula segments of the LUL were not treated to achieve incomplete occlusion of the upper lobes and to prevent lobar atelectasis

Wood DE et al. J Thorac Cardiovasc Surg 2007;133(1):65–73.
Ninane V et al. Eur Respir J 2012;39:1319–1325.

- Two RCTs, heterogeneous emphysema, QCT analysis for FI, lobar treatment, similar inclusion criteria → [illegible]

EMPROVE (Evaluation of the SVS for Emphysema to Improve Lung Function)
SVS:Control = 113:59

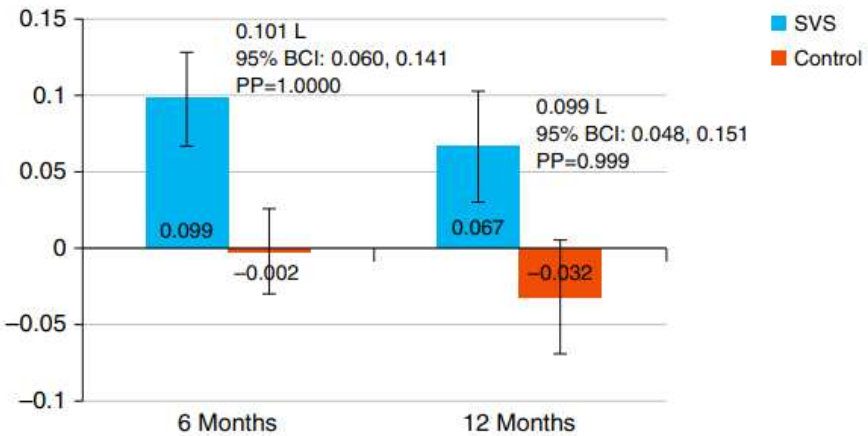


Figure 3. Change in FEV_1 at 6 and 12 months; data are shown as mean and 95% Bayesian credible interval (BCI). PP = posterior probability; SVS = Spiration Valve System.

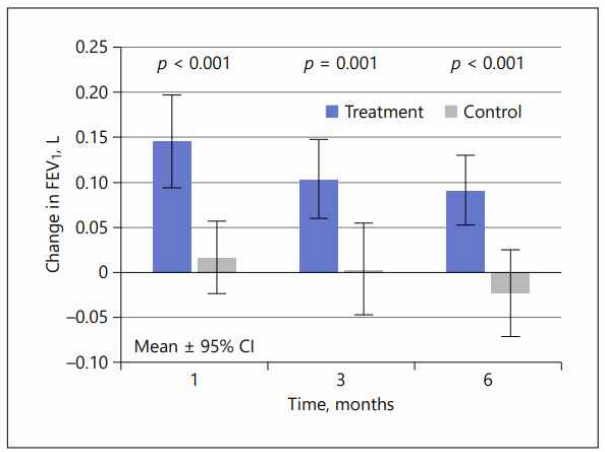


Fig. 4. Change in FEV_1 for the treatment and control arms. FEV_1, forced expiratory volume in 1 s.

REACH (Research to Assess SVS Safety and Effectiveness for the Treatment of Severe Emphysema in China)
SVS:Control = 72:35

Criner GJ et al. Am J Respir Crit Care Med 2019;200(11): 1354–62.
Li S et al. Respiration 2019;97(5):416–27.

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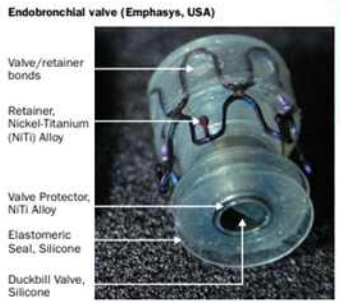

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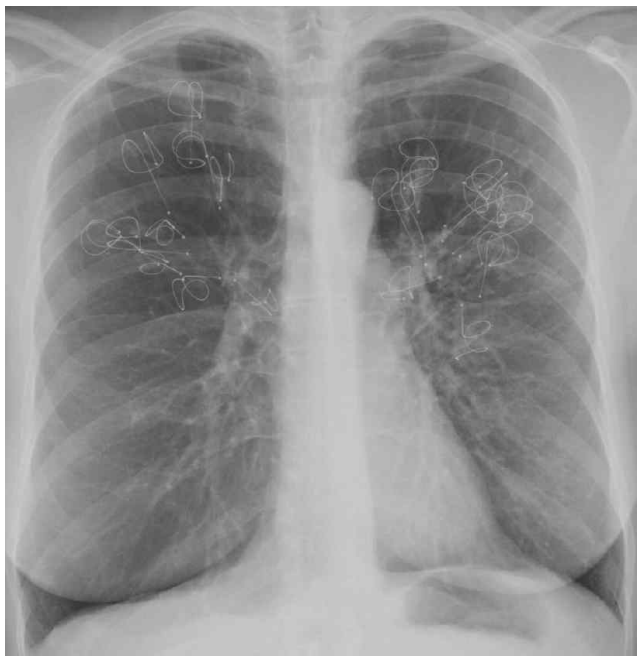
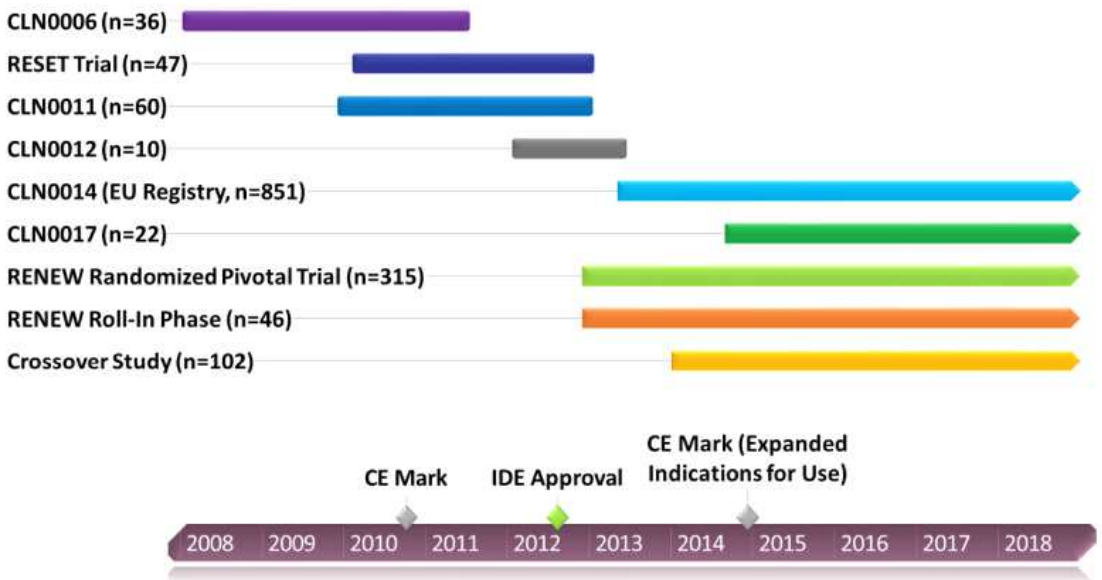
Lung volume reduction coils (LVRCs)



- Elevair™ Endobronchial Coils System (100 mm, 125 mm, 150 mm)
- Coil length was selected based on airway length assessed prior to insertion using a guidewire scored with radiopaque markers.
- 10 (8-14) coils are implanted for each lung (Under general anesthesia)
- The second procedure is performed within 4-8 weeks

Figure 6. PneumRx-Sponsored Clinical Studies of the ELEVAIR System



Panel Pack Sponsor Executive Summary, FDA Advisory Panel Meeting, June 14, 2018.

The RENEW trial

End point	Coil Treatment (n = 155)		Usual Care (n = 157)		Between-Group	P
	At 12 mo	Within-Group	At 12 mo	Within-Group		
6MWT, m	320 (243-388)	+10 (-33 to 45)	300 (233-350)	-8 (-40 to 26)	+14.6 (0.4 to ∞)	0.02
FEV_1, %	0.71 (0.58-0.88)	+4 (-6 to 16)	0.68 (0.54-0.82)	-3 (-9 to 4)	+7 (3.4 to ∞)	0.01
SGRQ	51.9 (49.5-54.4)	-8 (-10 to -6)	58.4 (55.9-60.9)	1 (-1 to 3)	-9 (-∞ to -6)	<0.001
RV, L	4.95 (4.75-5.14)	-0.41 (0.57 to -0.25)	5.28 (5.07-5.49)	-0.10 (-0.26 to 0.06)	-0.31 (-∞ to -0.11)	0.001

Within 12 mo	Coil Treatment	Usual Care	P
COPD AE	43 (28)	32 (20)	0.15
Pneumonia	31 (20)	7 (4)	<0.001
Pneumothorax	15 (10)	1 (1)	<0.001
Hemoptysis	4 (3)	0	-
Death	10 (6)	8 (5)	0.64

Rare complications – coil-related aspergilloma, BPF & penetration into pleural space

Sciurba FC et al. JAMA. 2016;315(20):2178–2189.

Thermal vapor ablation (TVA)

- Mechanism: Heated water vapor → thermal injury in airways → inflammatory response followed by fibrotic and atelectatic changes to induce volume reduction
- Theoretic advantages
  - CV(+) patients can be treated
  - The most diseased subsegments of the lung can be targeted allowing preservation of less diseased lung tissue, even if present in the same lobe.
  - No foreign body prostheses

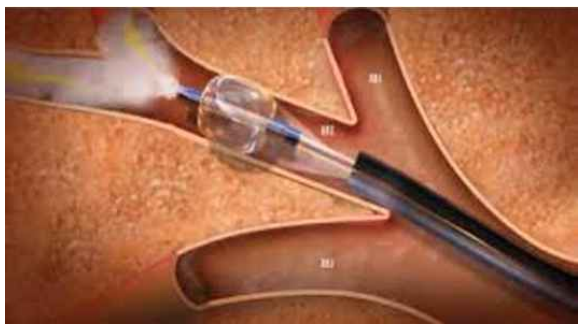
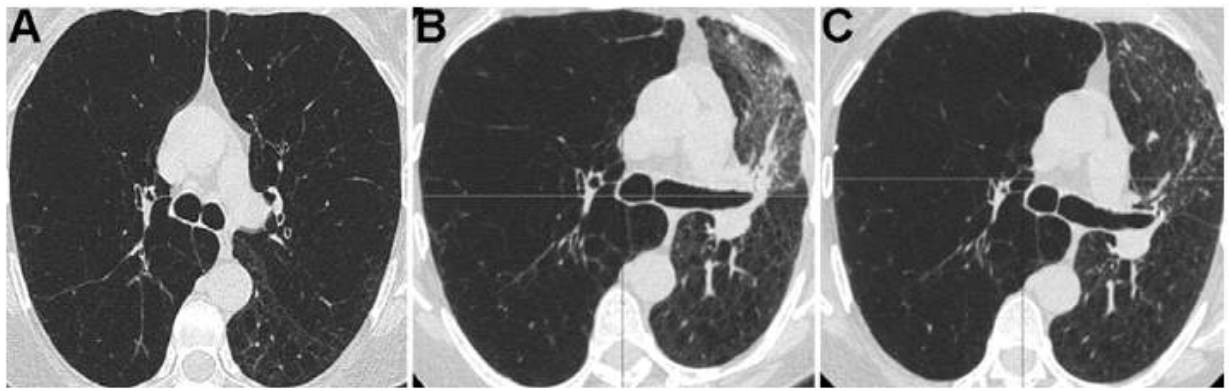


Fig 3. Chest computed tomography transverse slice example of left-sided unilateral bronchial thermal vapor ablation demonstrates loss of the target left upper lobe volume at (A) baseline, (B) 3 months, and (C) 6 months.



Snell GI et al. Ann Thorac Surg 2009;88:1993–1998.

The STEP-UP trial

(Sequential Staged Treatment of Emphysema with Upper Lobe Predominance)

***Figure 3*: Endpoints for pulmonary function, quality of life, and exercise tolerance in each trial group**

FEV_1=forced expiratory volume in 1 s. SGRQ=St George's Respiratory Questionnaire. 6MWT=6-min walk test.

	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.

***Table 6*: Serious adverse events and hospital admissions**

Herth FJ et al. Lancet Respir Med 2016;4(3):185–93.

Other than LVR

Bronchial rheoplasty for chronic bronchits (AJRCCM 2020)

Targeted lung denervation, AIRFLOW-2 (AJRCCM 2019)

Airway bypass track stent

Clinical pilot study (Ann Thorac Surg 2003)

EASE (Lancet 2011) : no sustained long-term effects

BioLVR

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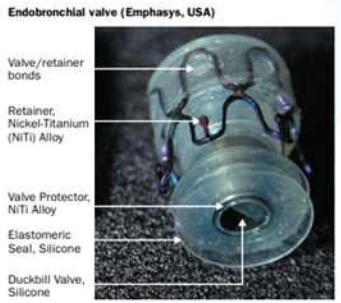

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Incomplete occlusion of the upper lobes (JTCVS 2007)

EMPROVE (AJRCCM 2019)
REACH (Respiration 2019)
: heterogeous emphysema, lobar treatment, similar effect and complications

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RENEW (JAMA 2016) : both upper lobes, regardless of CV

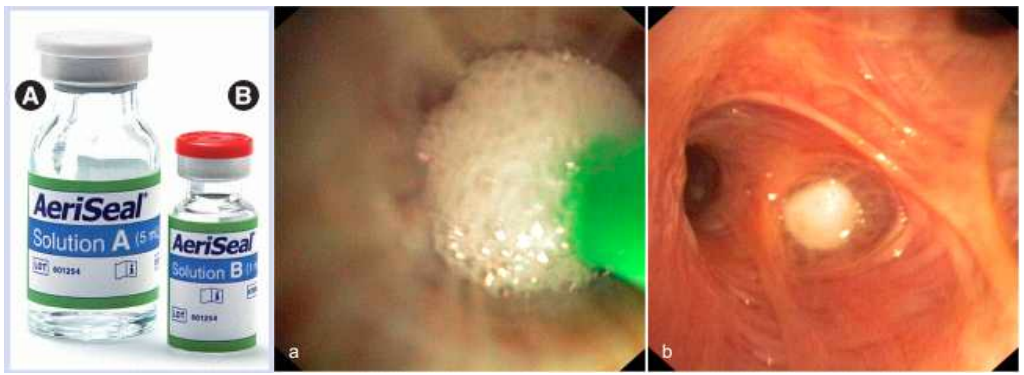
TVA

Clinical pilot study (Ann Thorac Surg 2009)

STEP-UP (Lancet Respir Med 2016)
: Subsegments can be targeted
: Pneumonitis

Biologic lung volume reduction (BioLVR)
(AeriSeal Emphysematous Lung Sealant (ELS))

- Fibrinogen + Thrombin = Hydrogel (polymerize in situ)
  : Delivered to the subsegmental bronchus and into the alveoli
  - →Localized inflammatory reaction: atelectasis, remodeling of emphysematous lung over 3 to 6 weeks
  - →Biodegradable complexes of poly-L-lysine and chondroitin sulfate
- Theoretic advantages
  - CV(+) patients can be treated
  - No implant remains in the body long-term, which may reduce the risk of infection, implant migration and tissue reaction.



Criner GJ et al. Am J Respir Crit Care Med 2009;179(9):791–8.

The ASPIRE trial

(AeriSeal System for Hyperinflation Reduction in Emphysema)

- The study was terminated prematurely for business-related reasons after 95 out of 300 planned patients were randomised.

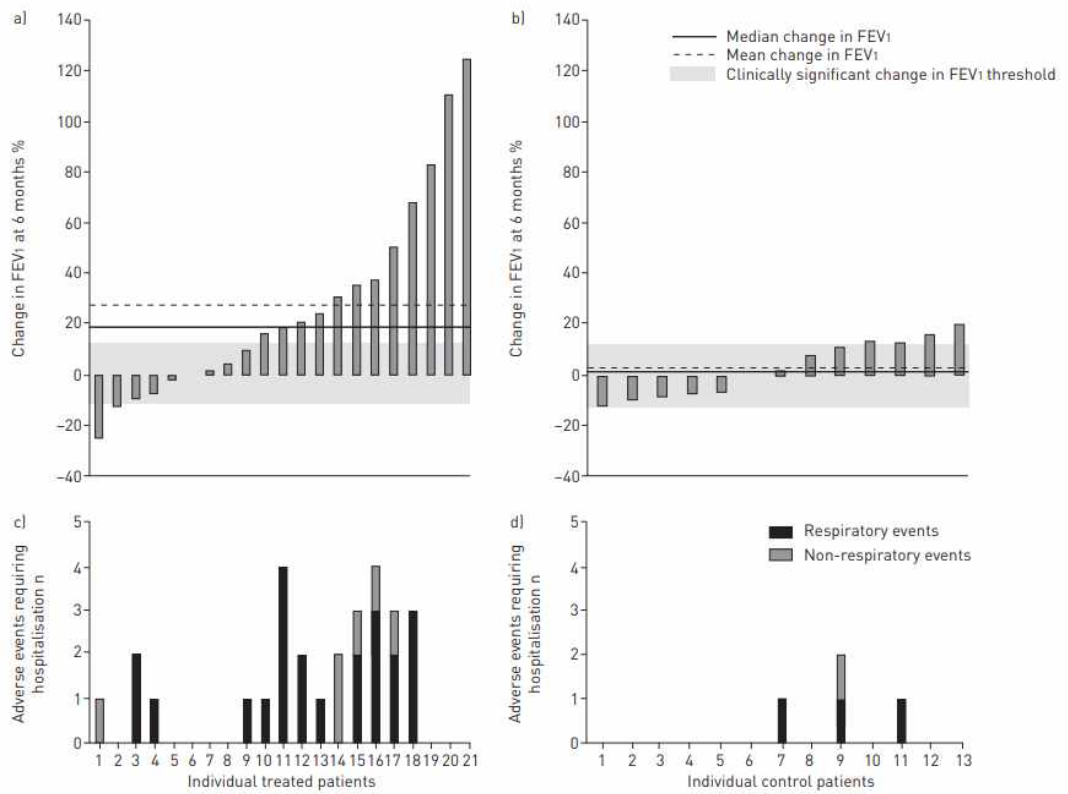
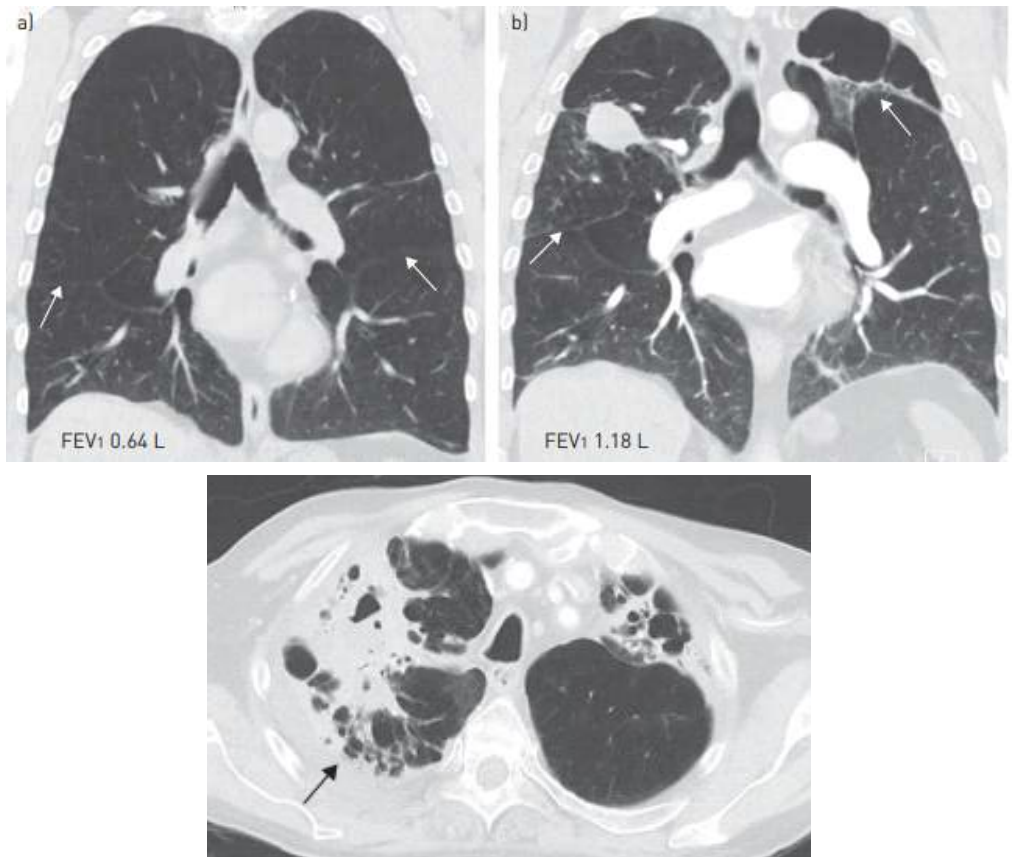


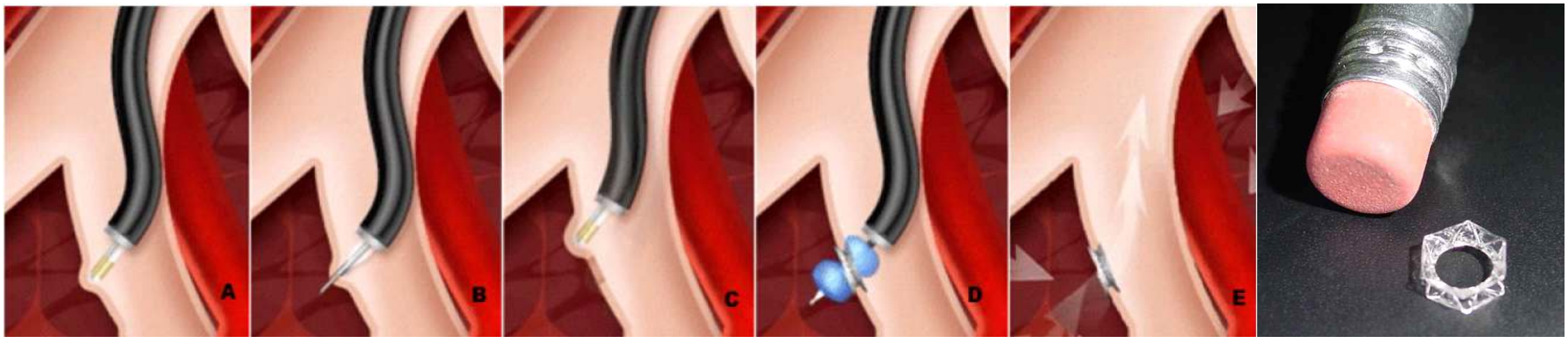
FIGURE 3 Percentage change in forced expiratory volume in 1 s (FEV1) from baseline to 6-month follow-up for a) treated patients and b) control patients. Each bar represents an individual patient. The regions outside the shaded zone indicate clinically significant changes in FEV1. Adverse events requiring hospitalisation for the corresponding individual c) treated patients and d) control patients.



Come CE et al. Eur Respir J 2015;46(3):651–62.

Airway bypass tract stent placement

- Creation of extra-anatomic bronchopulmonary passages is a potential therapeutic option for emphysematous patients with marked hyperinflation and severe homogeneous emphysema (ex vivo study with explanted human lungs from recipients undergoing lung transplantation)
- Paclitaxel-eluting stent to maintain patency of the bypass tracts (Broncus Technologies, Mountain View, CA)



Lausberg HF et al. Ann Thorac Surg 2003; 75: 393–98.

The EASE trial

(Exhale Airway Stents for Emphysema)

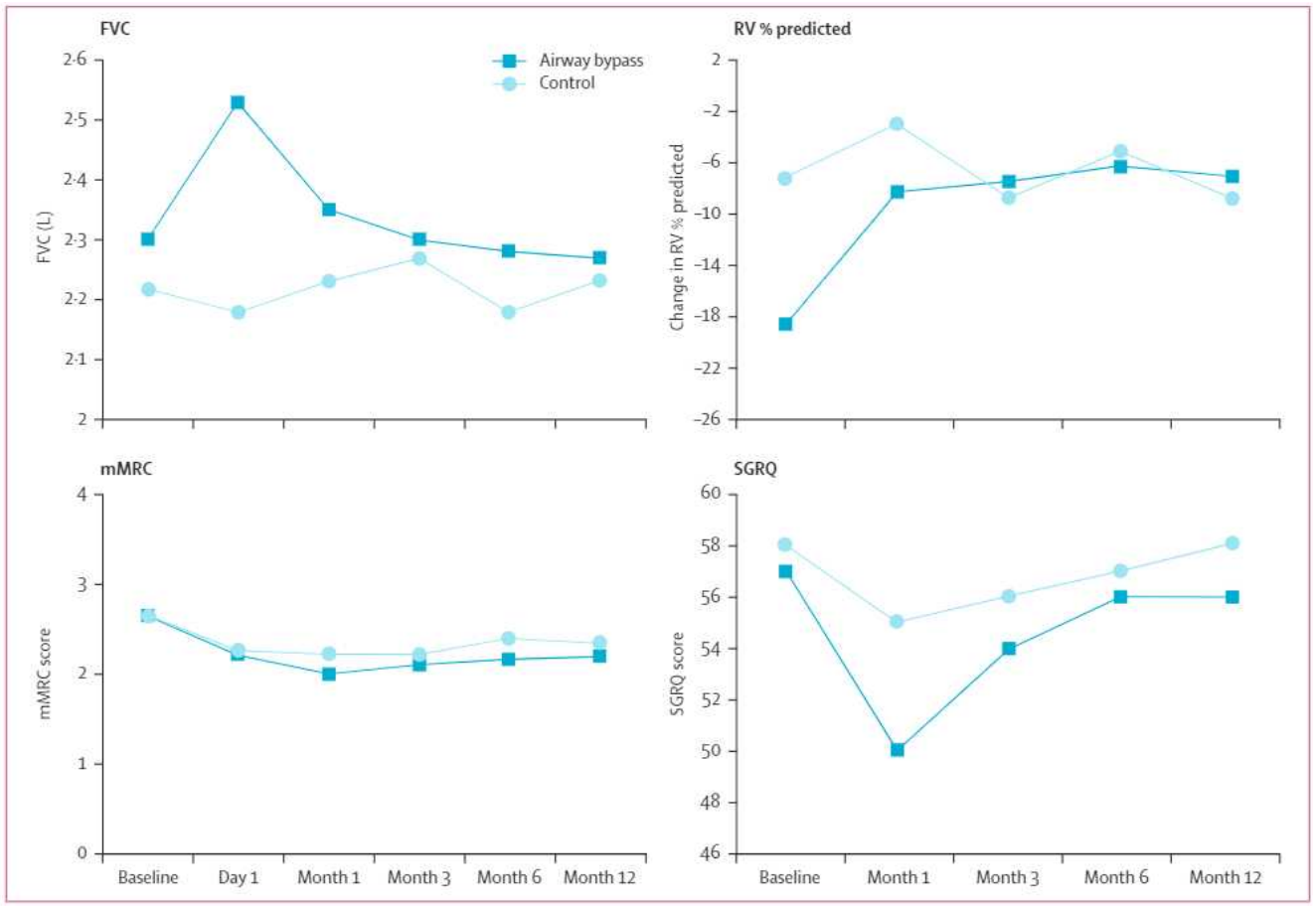


Figure 3: **Primary and secondary efficacy endpoints**
Data are mean values by follow-up visit. FVC=forced vital capacity. mMRC=modified Medical Research Council dyspnoea score. RV=residual volume. SGRQ=St George's respiratory questionnaire.

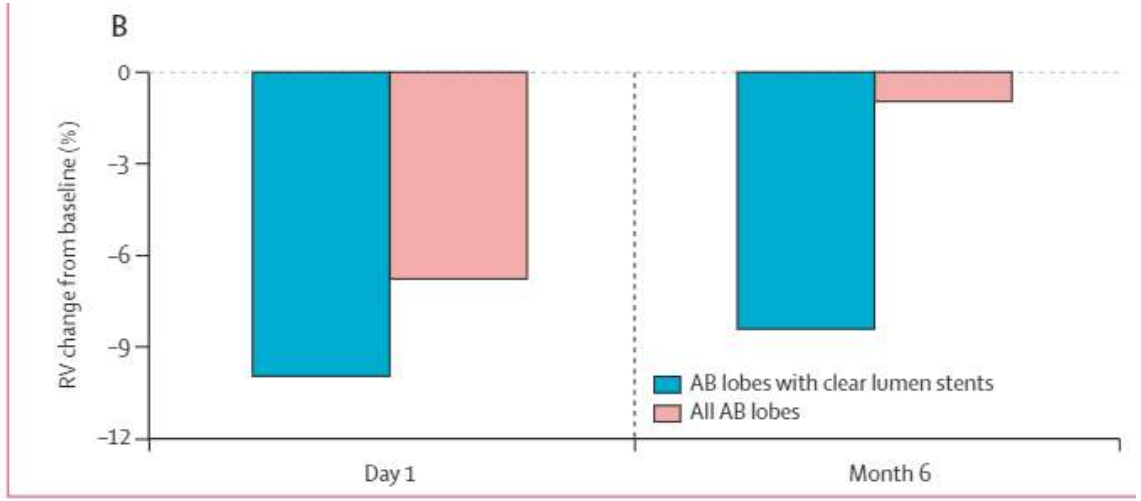


Figure 4: **CT-based lobar RV changes**
(A) RV changes by lobe. (B) RV changes in AB lobes with at least one clear visible stent. RUL=right upper lobe. RLL=right lower lobe. LUL=left upper lobe. LLL=left lower lobe. RV=residual volume. AB=airway bypass.

Despite the acute reduction in regional air trapping with an acceptable safety profile, the EASE trial failed to showed sustained long-term effects. Possible explanations included loss of stents from expectoration or occlusion from tissue debris.

Shah PL et al. Lancet 2011; 378(9795):997–1005.

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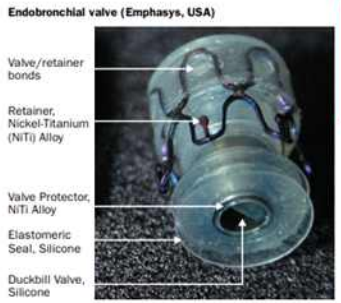

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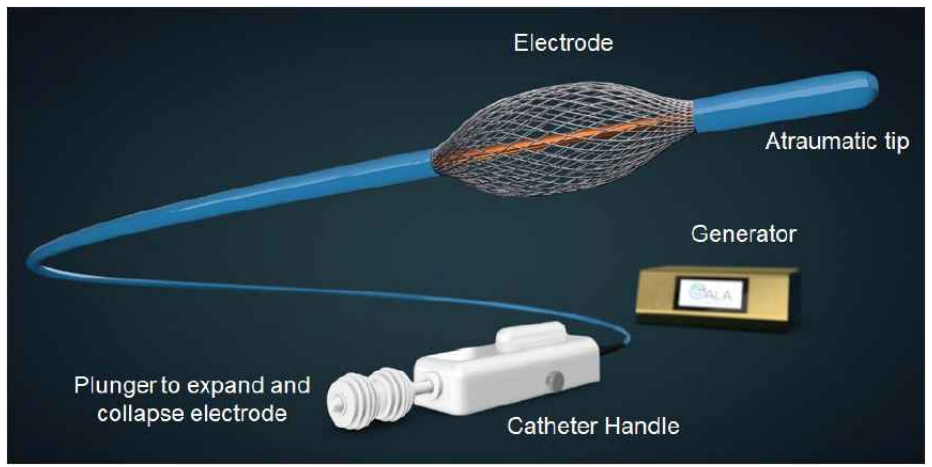
STEP-UP (Lancet Respir Med 2016)
: Subsegments can be targeted
: Pneumonitis

Bronchial rheoplasty (RheOx System, Gala Therapeutics) for treatment of chronic bronchitis

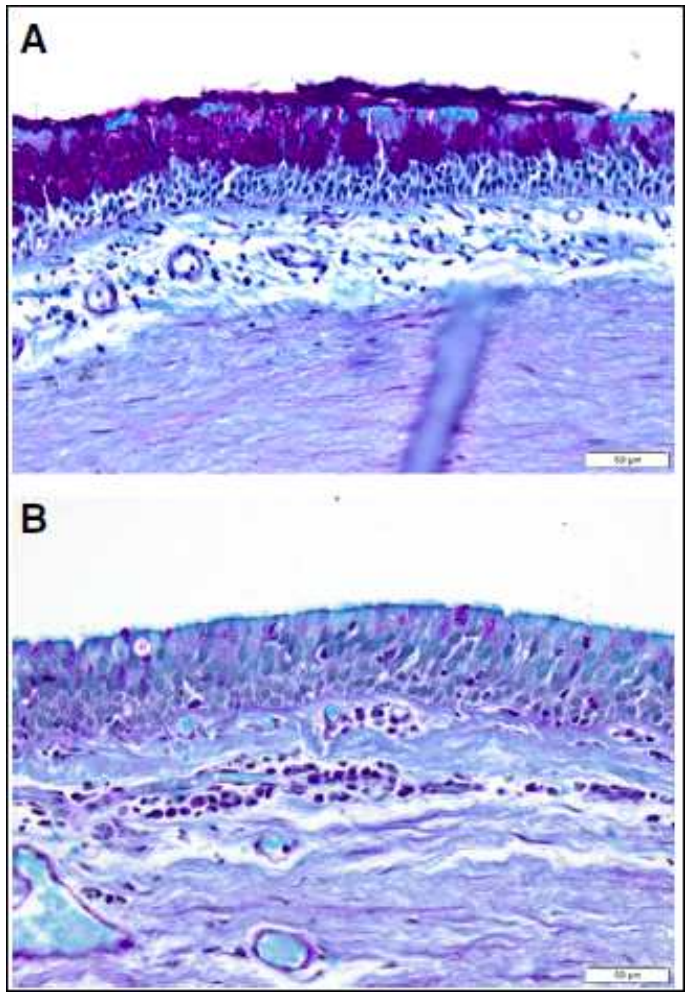
- Rheo = electrical current
- Bronchial rheoplasty: endobronchial catheter → ■□■◆▭◯●□◆● airways → epithelial ablation → regeneration of normalized epithelium

- The electrode is expanded to circumferentially contact the airway wall.
- The generator is activated to deliver energy to the airway over 5 seconds.
- From the subsegmental airways to the main carina.
- Rt lung → Lt lung at 1 month after the initial treatment.
- 43 ± 21 activations per lung.



Valipour A et al. Am J Respir Crit Care Med 2020;202(5):681–689.

12-month results (30 patients)



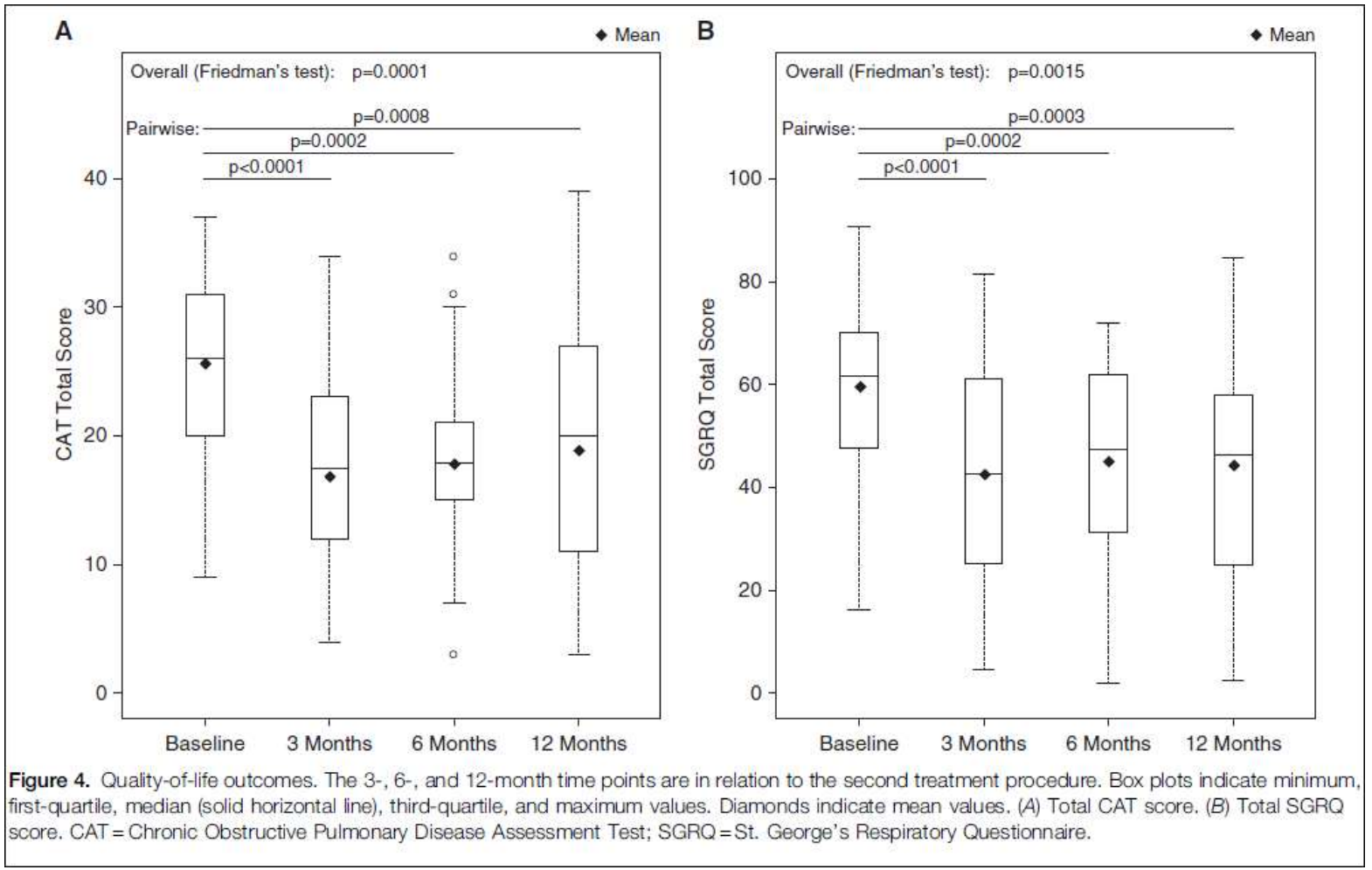


Figure 4. Quality-of-life outcomes. The 3-, 6-, and 12-month time points are in relation to the second treatment procedure. Box plots indicate minimum, first-quartile, median (solid horizontal line), third-quartile, and maximum values. Diamonds indicate mean values. (*A*) Total CAT score. (*B*) Total SGRQ score. CAT = Chronic Obstructive Pulmonary Disease Assessment Test; SGRQ = St. George's Respiratory Questionnaire.

Valipour A et al. Am J Respir Crit Care Med 2020;202(5):681–689.

Targeted lung denervation (TLD)
(Nuvaira TLD system)

- Parasympathetic activation in airways → bronchoconstriction & mucus production
  - Human research of vagotomy as a treatment for COPD (Thorax 1953;8:116-31)
  - Surgical denervation in patients with intractable asthma (J Thoracic Surg 1957;33:166-84)
  - Tiotropium, a long-acting muscarinic antagonist

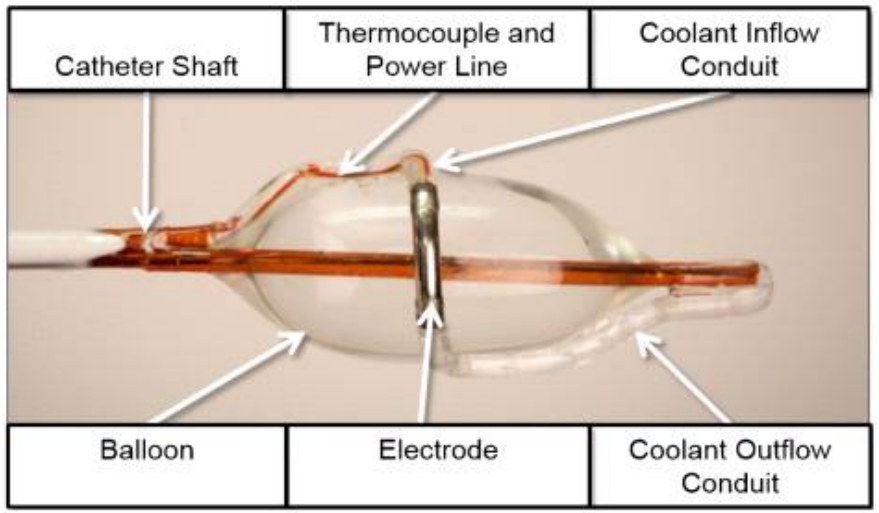
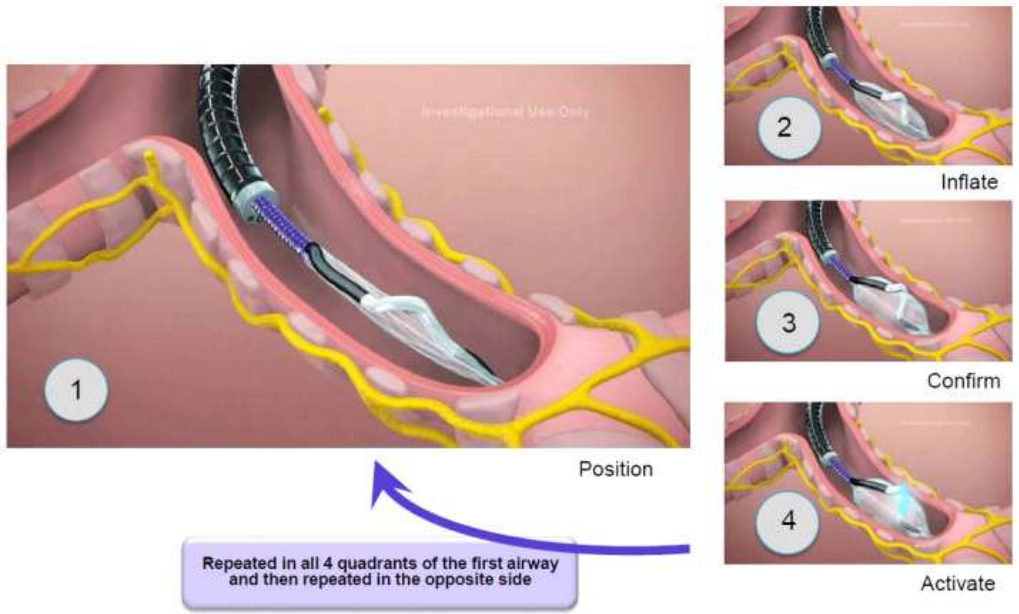


Figure 1 Description of the key components of the targeted lung denervation (TLD) catheter.



Slebos DJ et al. Thorax 2015;70(5):411–9.

The AIRFLOW–2 trial

(RCT with sham, double-blind; Moderate-Severe COPD)

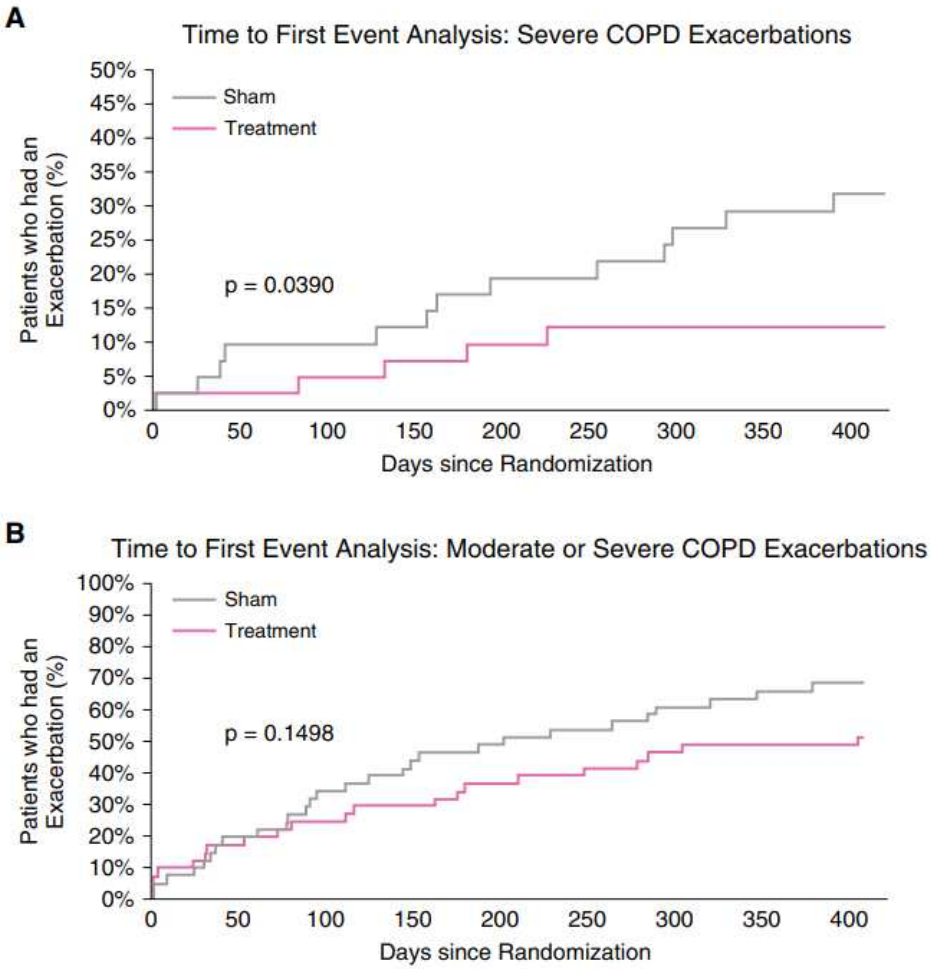


Figure 2. (*A*) Time-to-first-event analysis: severe chronic obstructive pulmonary disease (COPD) exacerbations. (*B*) Time-to-first-event analysis: moderate or severe COPD exacerbations.

Table 2. 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

Slebos DJ et al. Am J Respir Crit Care Med 2019;200(12):1477–1486.

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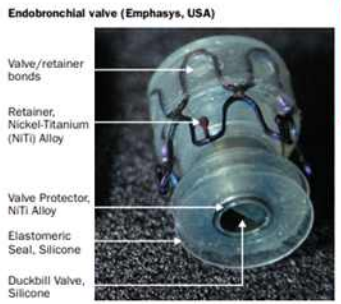

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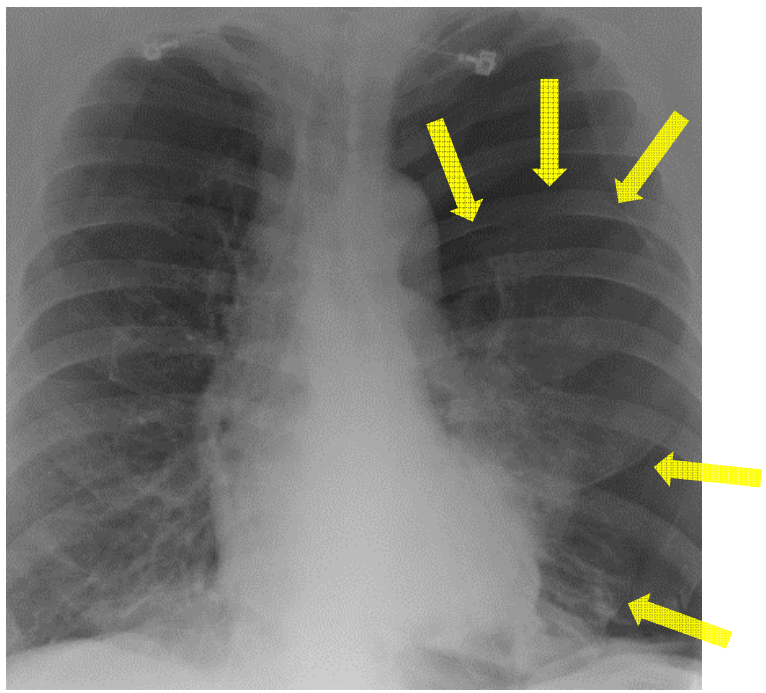
EBV for treatment of persistent air leaks : a systematic review

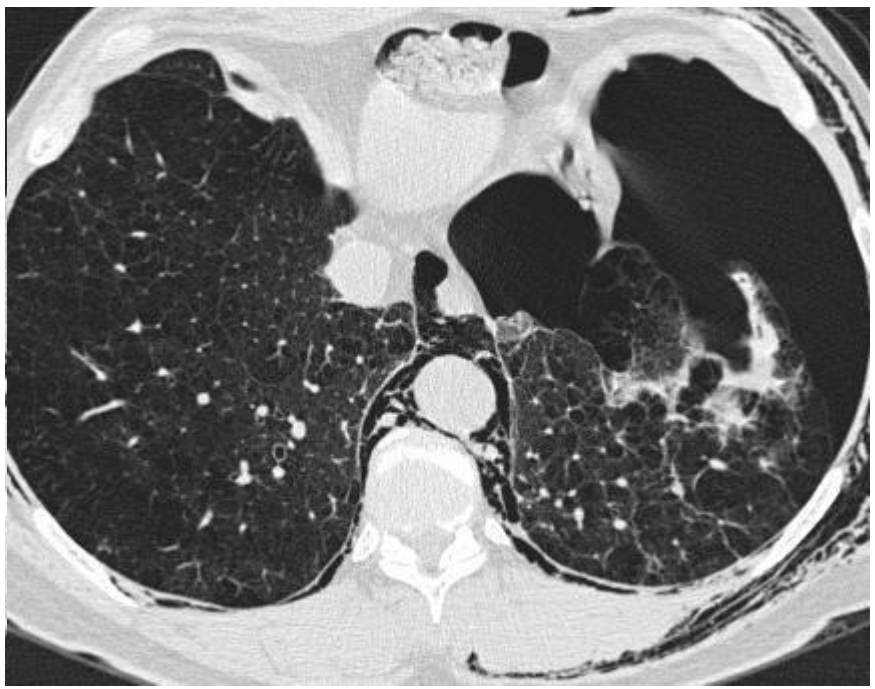
	Case reports (pts = 52, articles = 34)	Case series (pts = 156, articles = 10)
Age, yr	57 (18-93)	58-69
Causes of air leak	Pneumothorax: 35/52 (67%) Post-Op: 12/52 (23%) Empyema: 9/52 (17%) Fistula: 8/52 (15%)	COPD, ILD: 60/156 (38%), Malignancy: 51/156 (33%) Pneumothorax: 20/156 (13%) Pneumonia, empyema: 15/156 (10%) Post-Op: 12/156 (8%), Fungal, TB: 8/156 (5%)
Location of air leak	RUL: 17/52 (33%) LUL: 20/52 (38%) RML: 6/52 (12%) RLL: 6/52 (12%) LLL: 8/52 (15%)	RUL: 26/92 (28%) LUL: 33/92 (36%) RML: 6/92 (7%) RLL: 13/92 (14%) LLL: 7/92 (8%)
Duration of air leak before EBV insertion, days	15 (3-2520)	8-20
No. of EBV per patient	2 (1-8)	1.4-4
Duration of air leak after EBV insertion	< 1 day: 31/50 (62%) 1-2 days: 6/50 (12%), > 2 days: 13/50 (26%)	1-6 days
Outcomes	Recurrence: 3/50 (6%)	Complete resolution: 104/155 (67%) Reduction: 39/155 (25%) No change: 5/155 (3%), Recurrence: 14/156 (9%)
Complications	Migration of EBV: 2/50 (4%) Death, not related to EBV: 3/50 (6%)	Death, not related to EBV: 2 Pneumonia: 1
Removal of EBV	20/50 (40%)	90/155 (58%) Mean days to EBV removal: 23-138

Ding M et al. Respir Res. 2017;18(1):186.

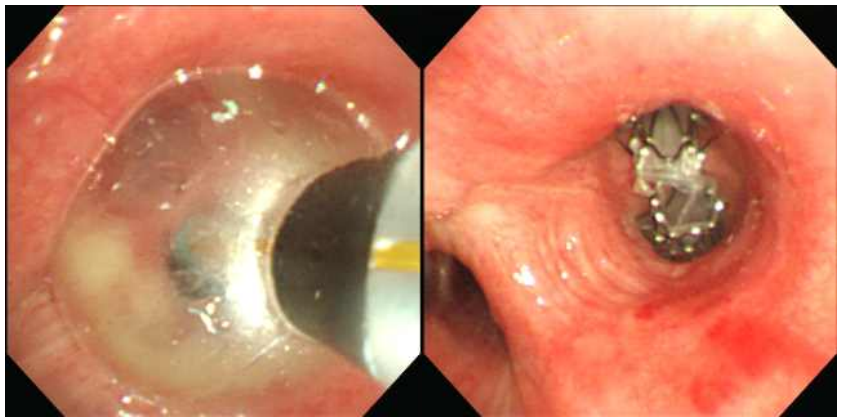
Case 1. Persistent air leak after pneumothorax – Medical history, CXR, and CT

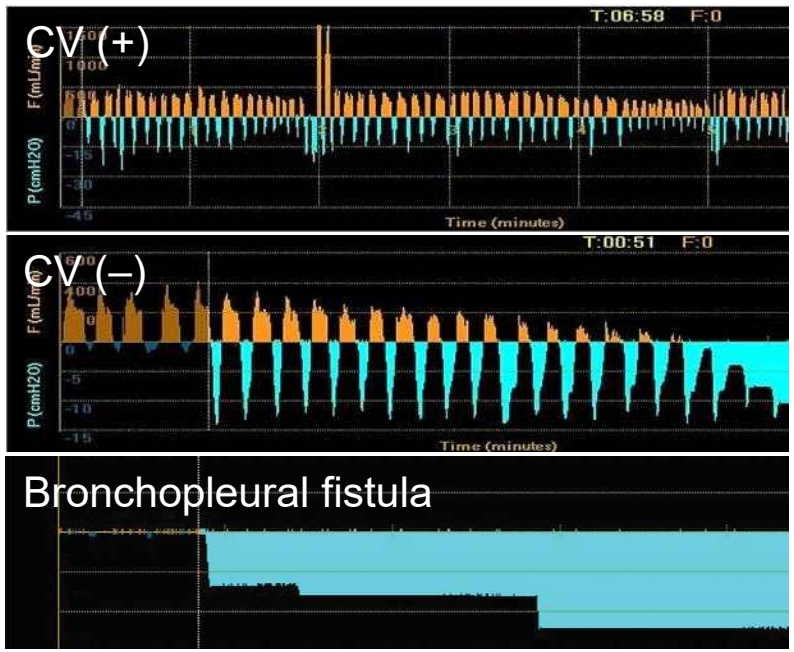
- M/55, Current smoker (2 × 35 = 70 PY)
- 5개월전 FEV_1/FVC 30%, FEV_1 33%, FVC 86%, DLCO 46%, RV 269%
- 기흉 19일째 본원 전원, 기흉 25일째 EBV insertion 시행

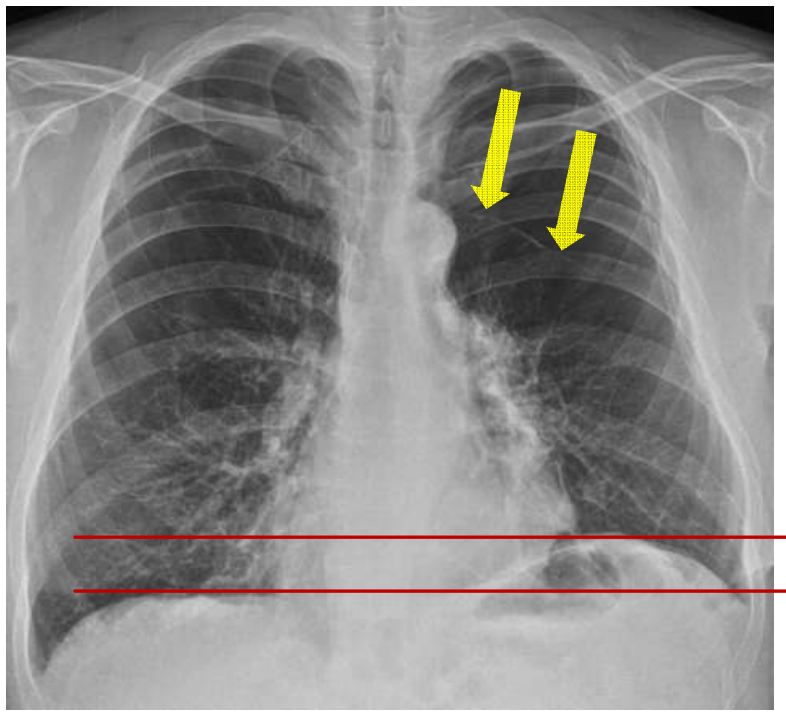




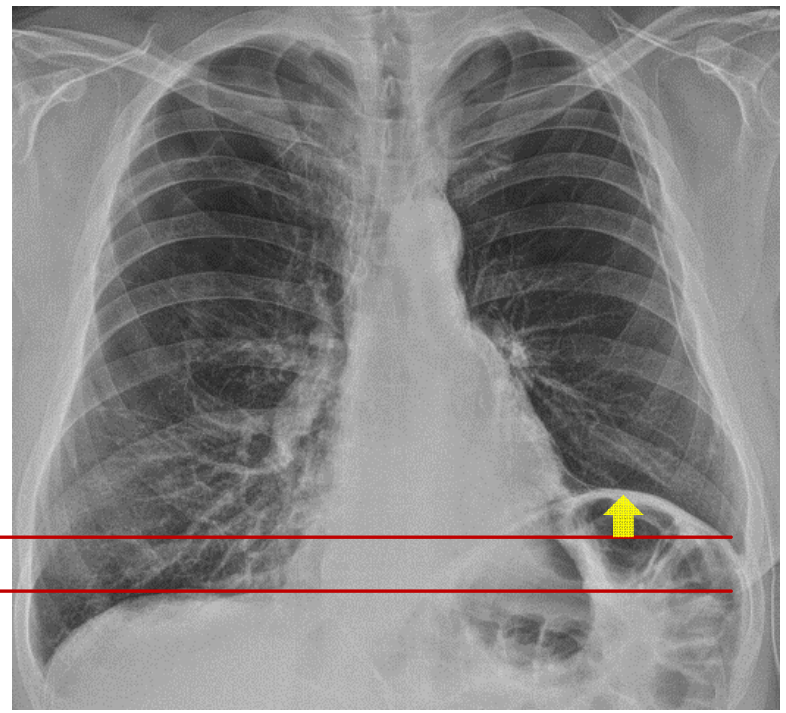
Case 1. Persistent air leak after pneumothorax – Bronchoscopy, f/u CXR





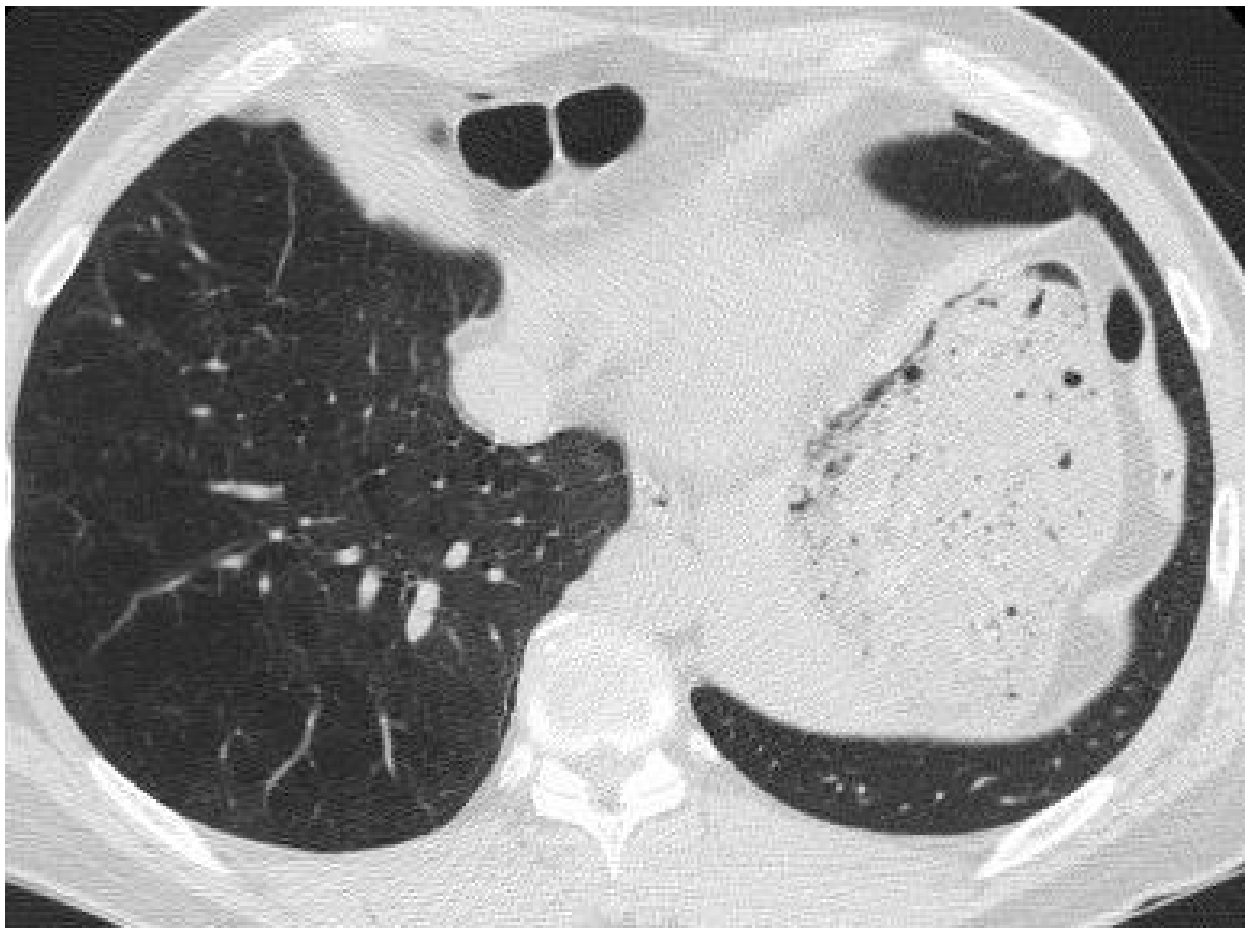


시술 직전



시술 직후

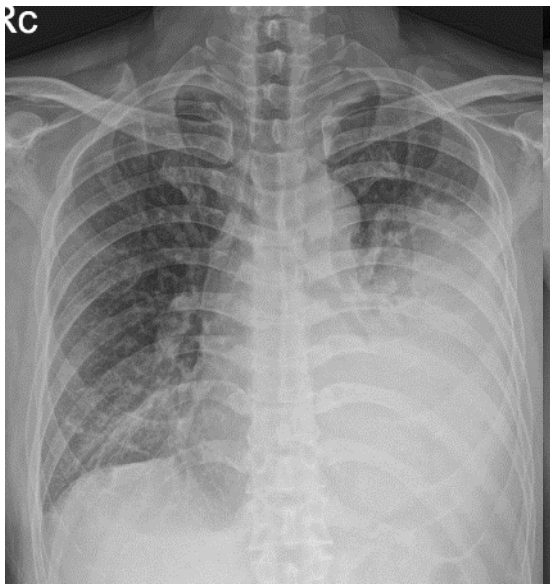
Case 1. Persistent air leak after pneumothorax – Bronchoscopy, f/u CXR



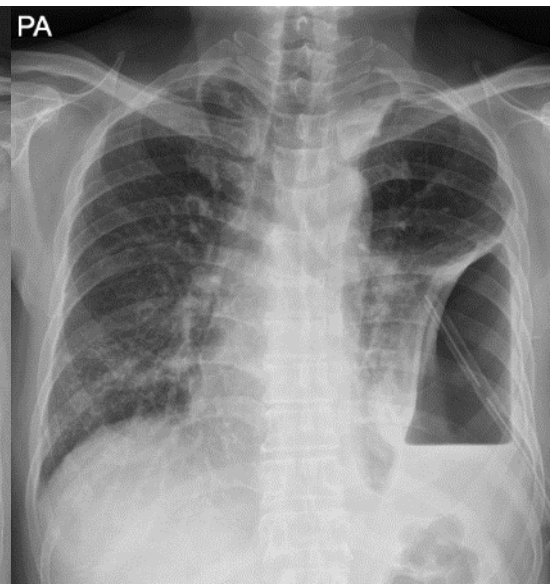
시술 2일째 Chest tube 제거 후 CT

Case 2. BPF with unsuccessful surgical correction – Medical history, CXR, and CT

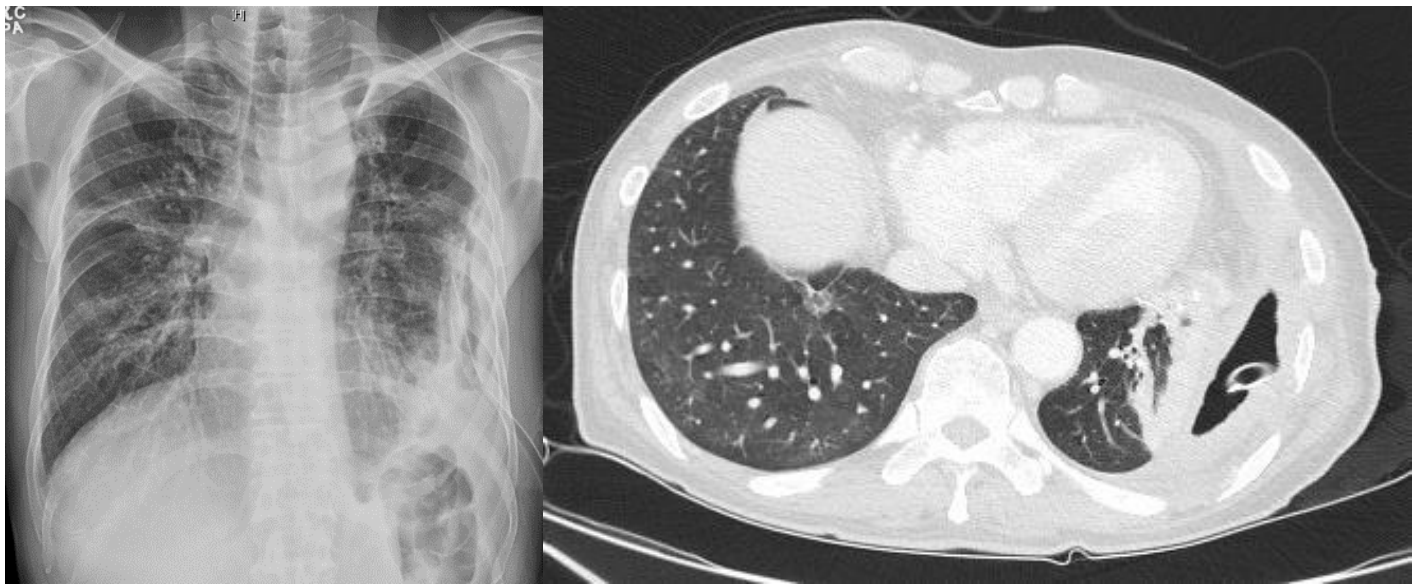
- M/63, Empyema (ESBL(–) *Klebsiella pneumoniae*) → Chest tube insertion 1달째 Heimlich bag으로 교체 후 퇴원
- 2달째 VATS decortication & surgical correction
- 3달째 3-5일 간격으로 3차례 추가 surgical correction 시도 (Neoveil & glue application) → air leak 지속
- 마지막 수술 시도 1주 뒤 EBV insertion



첫 내원 당시

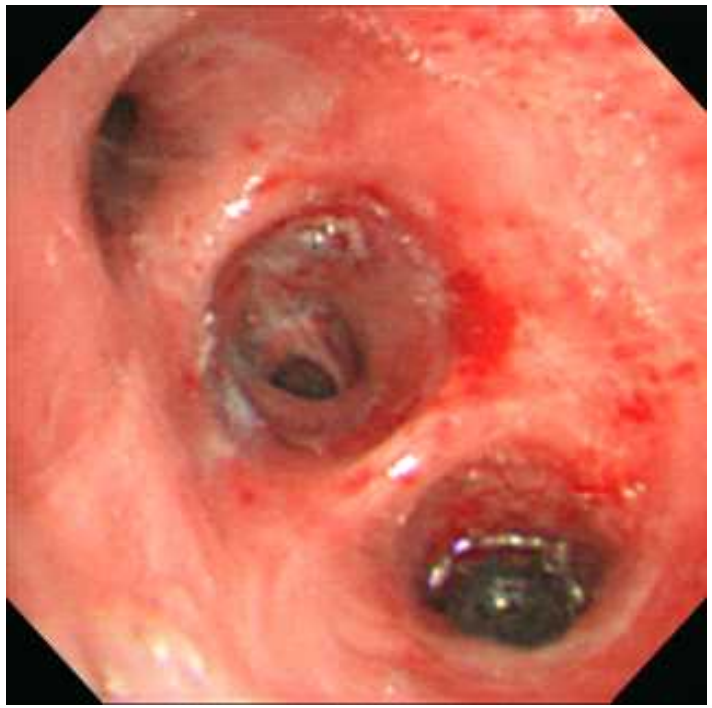


1달째 퇴원 당시

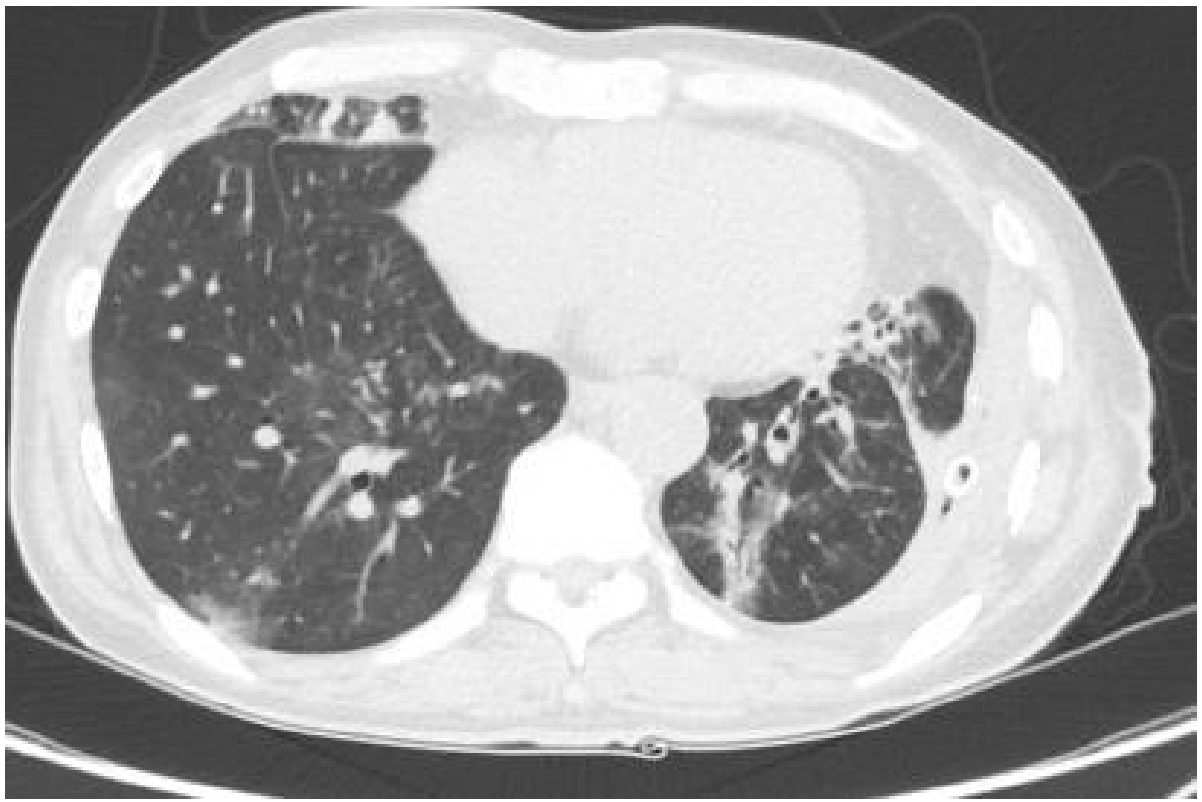


3달째 EBV 직전

Case 2. BPF with unsuccessful surgical correction – Bronchoscopy, and f/u CT

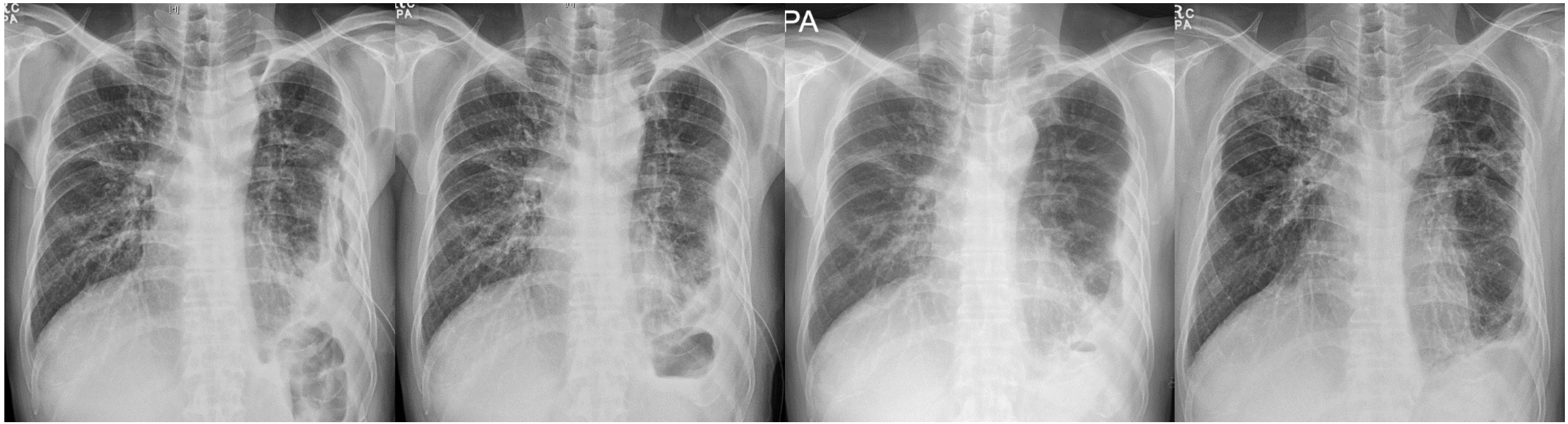


One EBV in LB4-5



1주 뒤 CT

Case 2. BPF with unsuccessful surgical correction – f/u CXR



3달째 EBV 직전

EBV 삽입 1주 뒤

EBV 삽입 1달 뒤
Chest tube 제거

2.5년 뒤

Summary

- Bronchoscopic LVR with one-way valves is a guideline treatment option for patients with advanced emphysema that is supported by extensive scientific data.
- The most important factor to success the procedure – 'Patient selection'
  - FEV_1 15–50%, RV > 175%, TLC > 100%

	Patient selection							
	Emphysema phenotype		Collateral ventilation		Target lobe		Removable (Reversible)	Main S/E
	Hetero	Homo	(–)	(+)	Upper	Lower		
Valve	☻	▲	☻	X	☻	☻	☻	Pneumothorax
Coil	☻	☻	☻	☻	☻	☻	▲	Pneumonia, Pneumothorax
Vapor	☻	X	☻	☻	☻	X	X	COPD AE, Pneumonia

- EBVs for treatment of persistent air leaks – a possible therapeutic option