Interventions for COPD

Gerard J. Criner, M.D.

Professor and Chair, Department of Thoracic Medicine and Surgery

Lewis Katz School of Medicine at Temple University

Philadelphia PA

Presenter Disclosures

Gerard J. Criner, M.D.

Honoraria: None

Grants received: NIH-NHLBI, PA-DOH,GSK, Boehringer- Ingelheim, Novartis, Astra Zeneca, Respironics, MedImmune, Actelion, Forest, Pharmaxis, Pulmonx, Aeris, PneumRx, Pearl, Spiration, Broncus

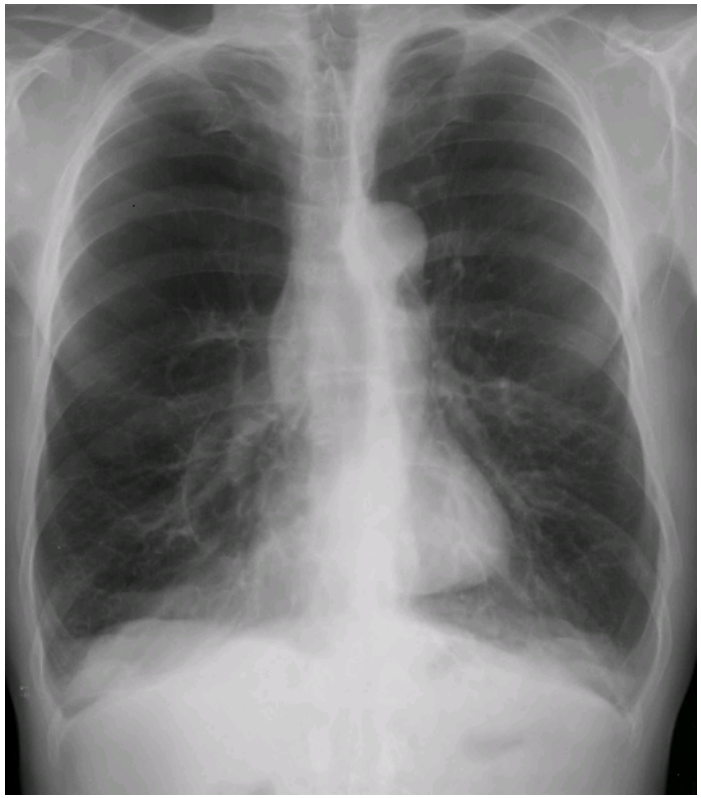
Grants pending: NIH-NHLBI, GSK, Astra Zeneca, Boehringer-Ingelheim, Nuvaira

Consultation: Consultation: Amgen, AstraZeneca, Boehringer Ingelheim, Broncus Medical, CSA Medical, Eolo Medical, Gala Therapeutics, GlaxoSmithKline, Helios Medical, Merck, Medtronic, Mereo BioPharma, NGM Biopharmaceuticals, Olympus, PhilipsRespironics, PulmonX, Respivant Sciences, VeronaPharma

Equity Interest: HGE Health Care Solutions

Hyperinflation In Emphysema

- Hyperinflation: devastating & common complication of COPD; especially emphysematous phenotype
  - Decreased Exercise Performance
  - Impaired Respiratory Muscle and Chest Wall Mechanics
  - Increased Breathlessness, Decreased Quality of Life
  - Prolonged Respiratory Failure Requiring Mechanical Ventilation
  - Impaired Cardiac Function
  - Increased Mortality (IC/TLC)



Bronchoscopic Lung Volume Reduction

- Targeted Lobe Atelectasis
  - One–way endobronchial valves
  - Self-activating coils
- Targeted Destruction & Remodeling of Emphysematous Tissue
  - Biological Lung Volume Reduction
  - Bronchoscopic Thermal Vapour Ablation (BTVA)
- Bypass Tract Stenting/Transpleural Ventilation
  - Endobronchial stents
  - Modified external chest tubes

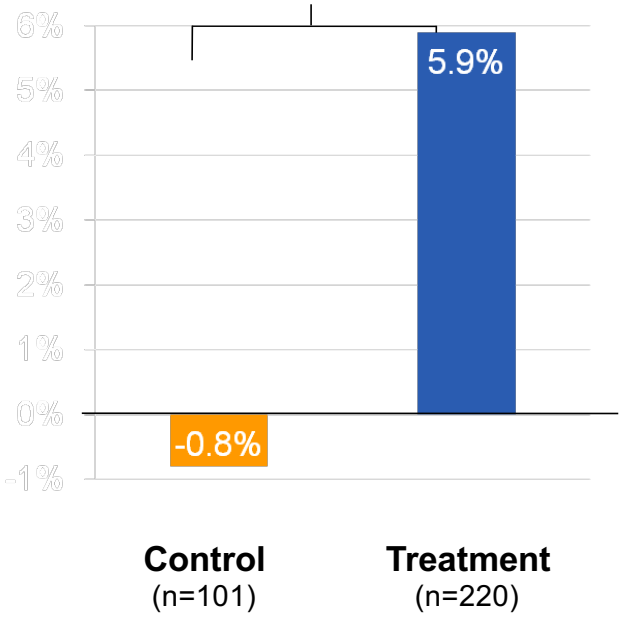
Endobronchial Valve for Emphysema PalliatioN Trial (VENT) Pivotal Trial

6 months : Primary Endpoints

FEV_1 % Change

Δ = 6.7%

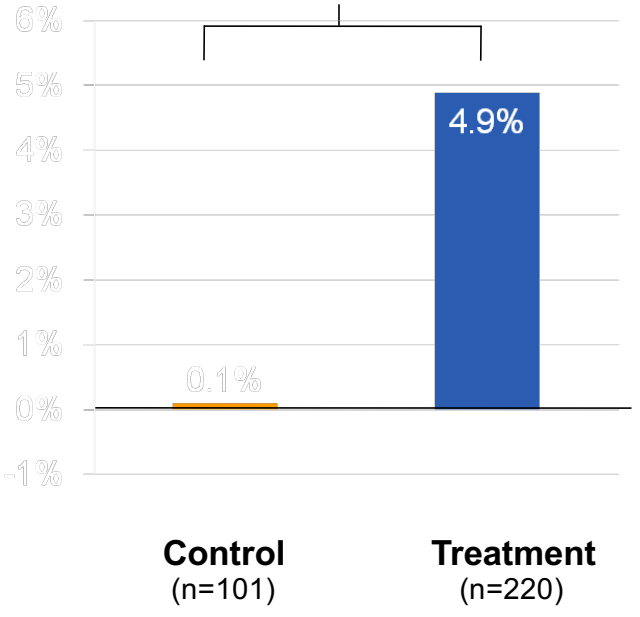
p = 0.0084



6MWT % Change

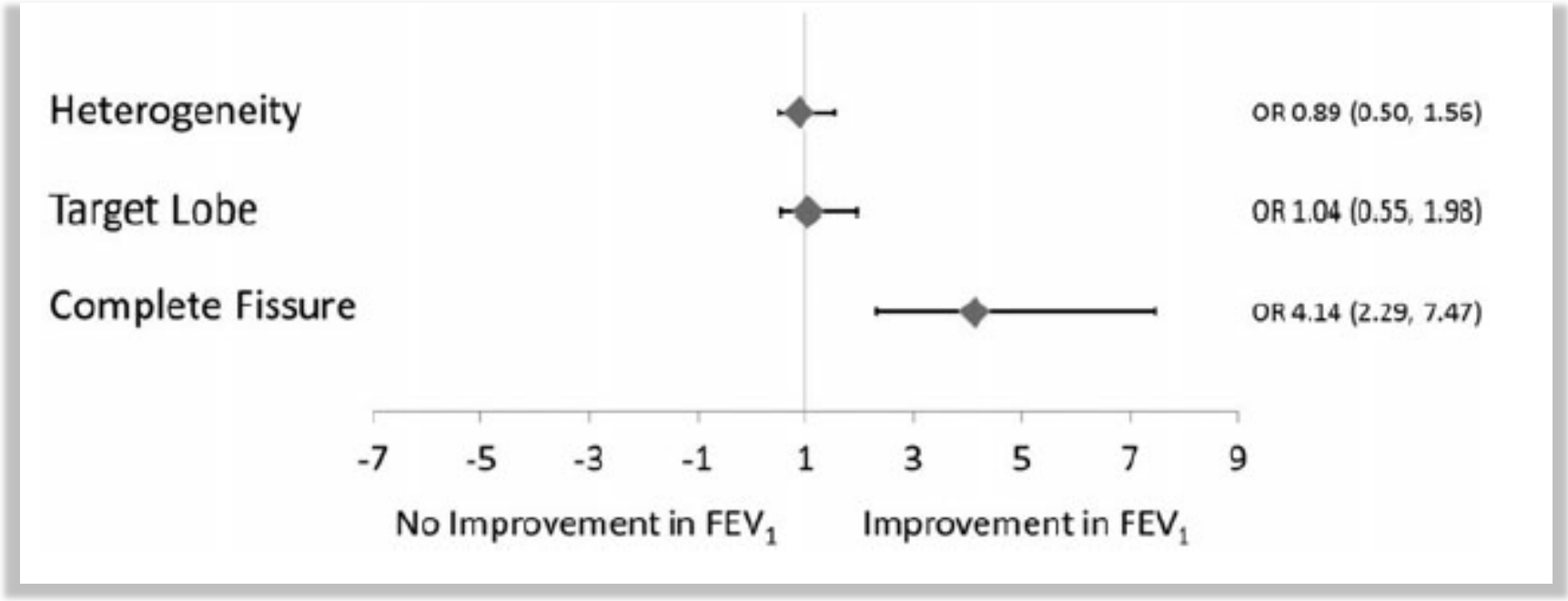
Δ = 4.8%

p = 0.0171



Sciurba, NEJM, 2010

Predictors of Successful Treatment

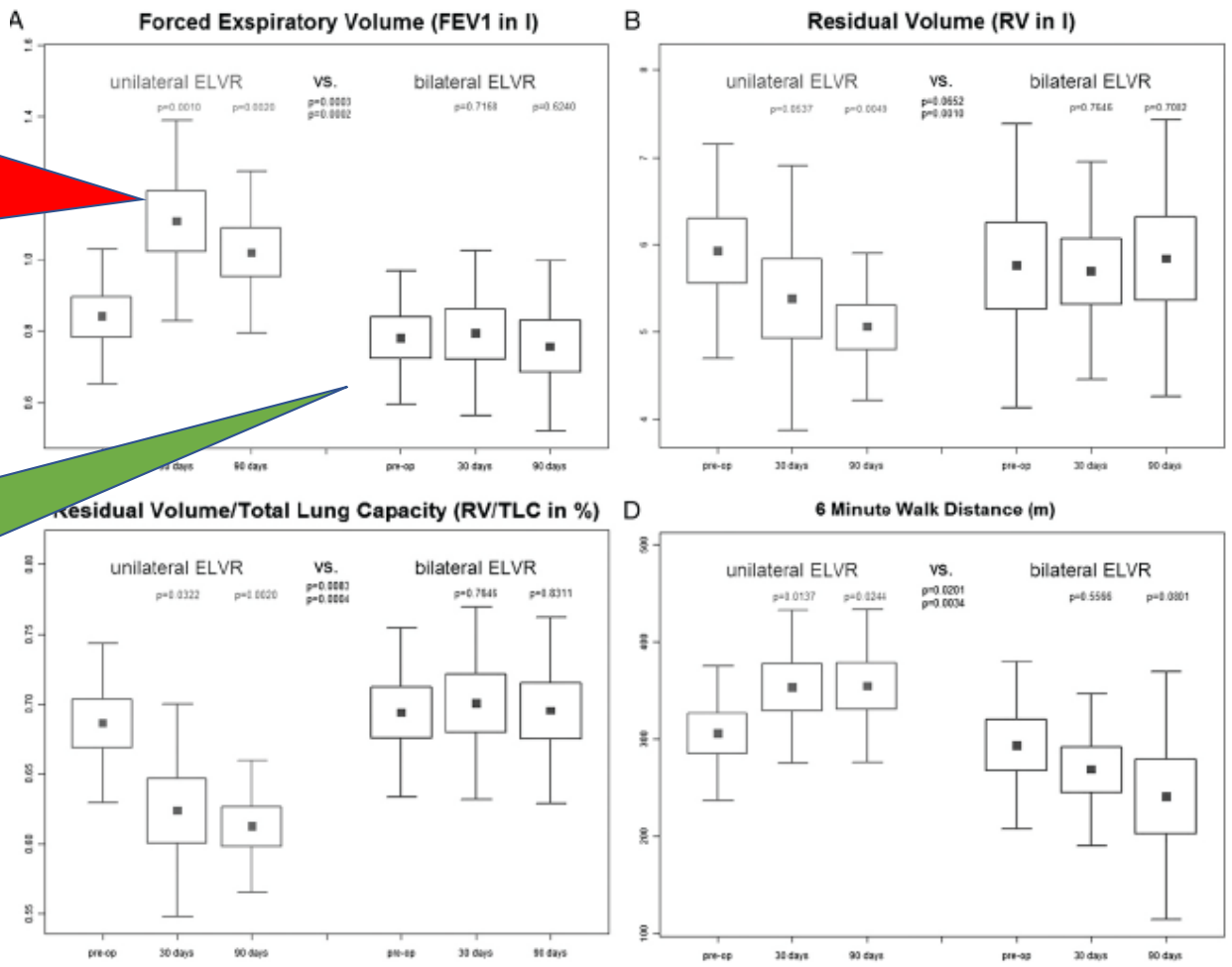


Liberator, COPD 2016

Complete Unilateral vs Partial Bilateral ELVR

Unilateral EBV with Total Lobar Occlusion

Bilateral Non-occlusive EBV

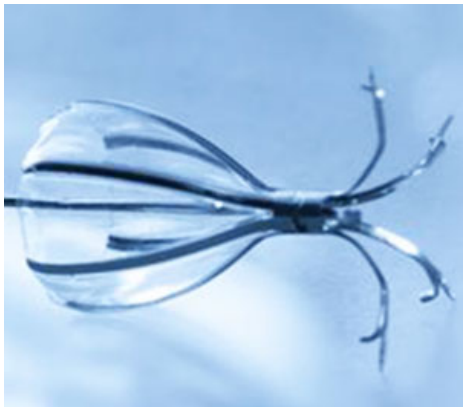


Eberhardt, Chest, 2012

Multicentered RCTs of Bronchoscopic Lung Volume Reduction with Total Lobar Occlusion for Heterogenous Emphysema

TRANSFORM

LIBERATE



REACH

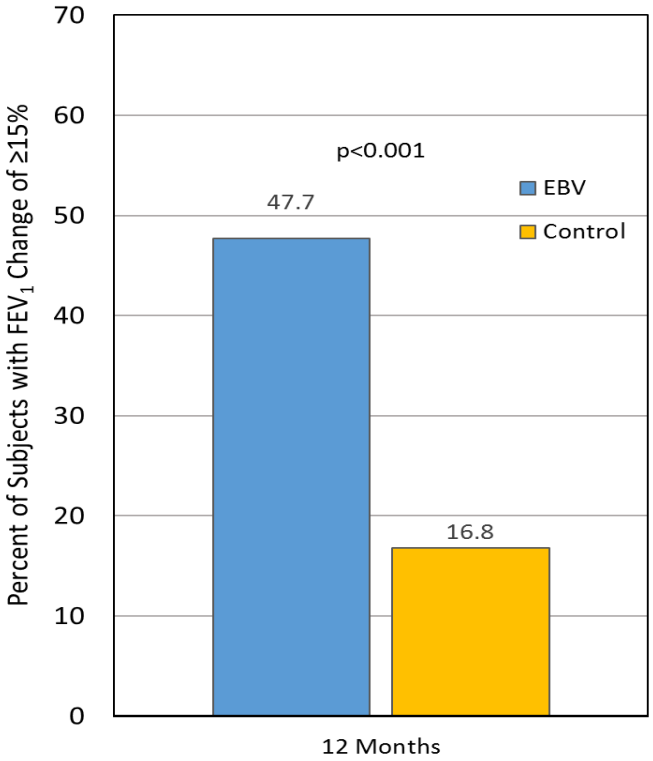
EMPROVE

Important Differences Between the Two Pivotal Studies

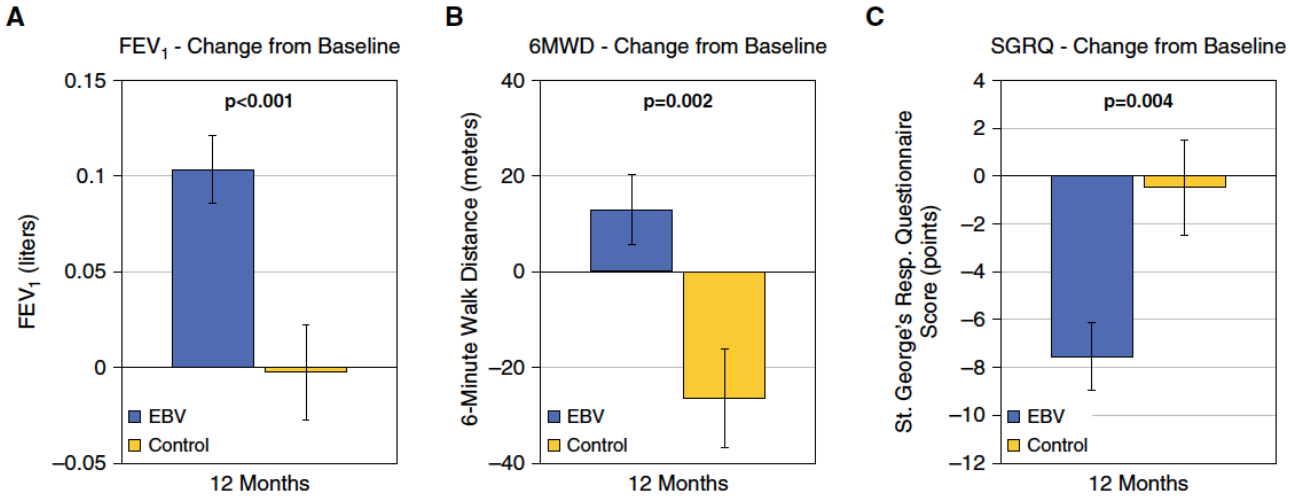
	LIBERATE	EMPROVE
FEV_1, %Pred	15-45	15-45
TLC, %pred	≥ 100	≥ 100
RV, % pred	≥ 175	≥ 150
6 MWD	6MWD 100-500m	6MWD ≥ 140M
% emphysema target lobe	≥ 50 (-910)	≥ 40 (-920)
% Heterogeneity (tx-not tx ipsilateral)	≥15	≥10
Lobar Occlusion Predictor	Target lobe with little or no collateral ventilation (Chartis Assessment)	FI ≥ 90% by HRCT
Primary Outcome	% ≥ 15% FEV_1	Mean FEV_1 Δ (6mths-baseline)
Duration	12 months	6 months

LIBERATE: Primary and Secondary Outcomes

Primary Outcome

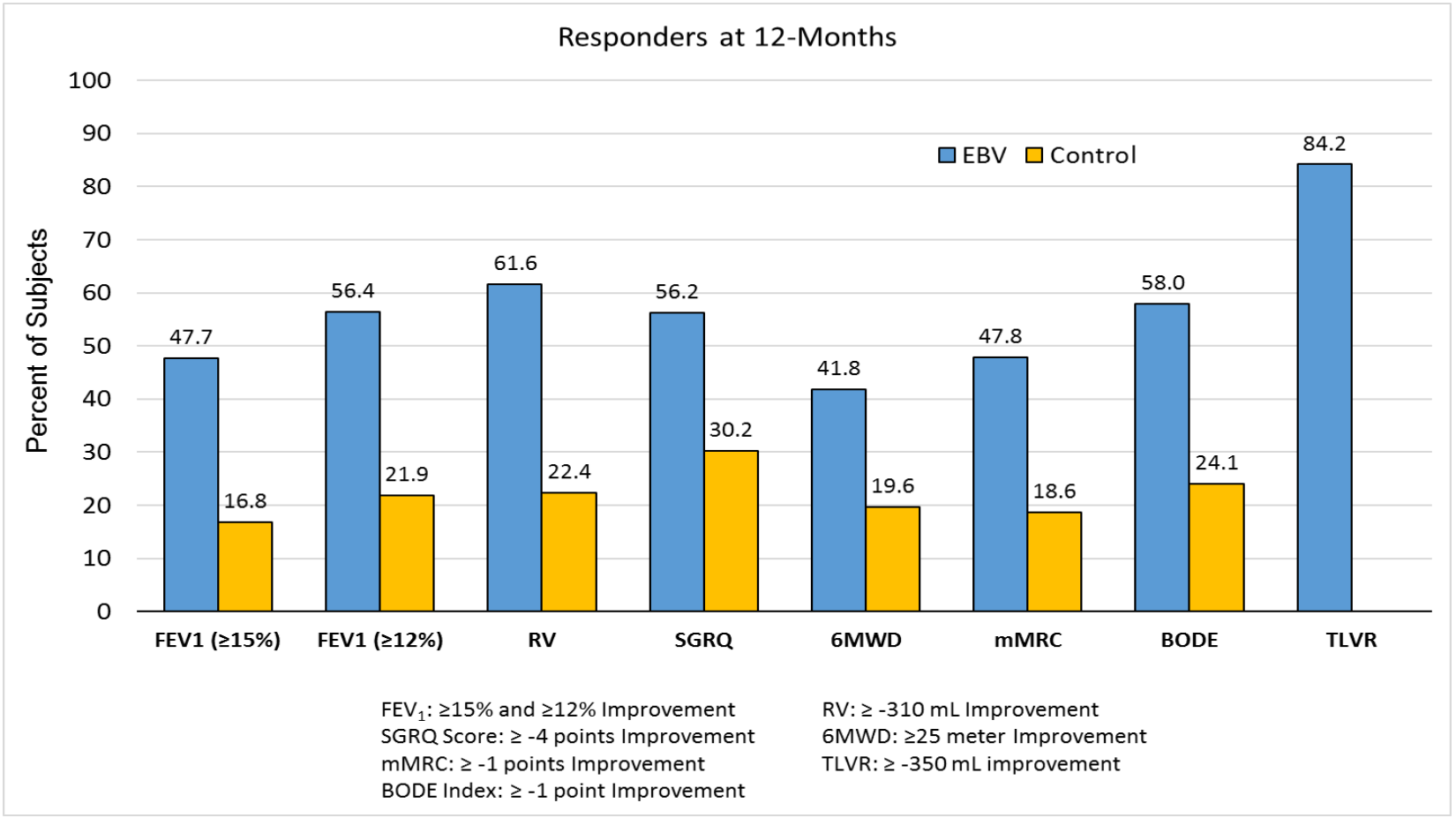


Secondary Outcomes



Criner, AJRCCM, 2018

Responder Rates for Key Outcomes



Criner, AJRCCM, 2018

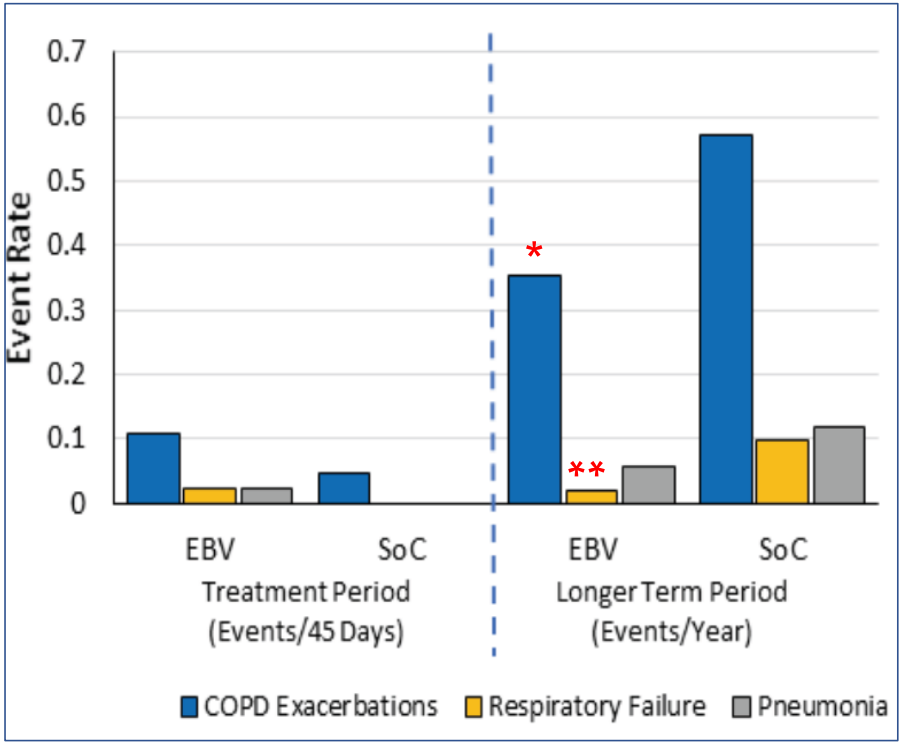
Serious Adverse Events

Serious Adverse Events Occurring in at Least 3.0% of Subjects in Either Group

	Treatment Period Day of Procedure/Randomization to 45 Days		Longer-Term Period 45 Days from the Study Procedure/Randomization until 12-month Visit Date	
	EBV (N=128)	SoC (N=62)	EBV (N=122)	SoC (N=62)
Death	4 (3.1%)[a]	0 (0.0%)	1 (0.8%)	1 (1.6%)
Pneumothorax	34 (26.6%)*	0	8 (6.6%) *Includes 5 pneumo-thoraces from revision procedures*	0
COPD exacerbation	10 (7.8%)	3 (4.8%)	28 (23.0%)	19 (30.6%)
Pneumonia	1 (0.8%)	0	7 (5.7%)	5 (8.1%)
Respiratory failure	2 (1.6%)	0	1 (0.8%)	2 (3.2%)
Arrhythmia	0	0	1 (0.8%)	2 (3.2%)
Diverticulitis	0	0	1 (0.8%)	2 (3.2%)

* P<0.05

Adjudicated Events

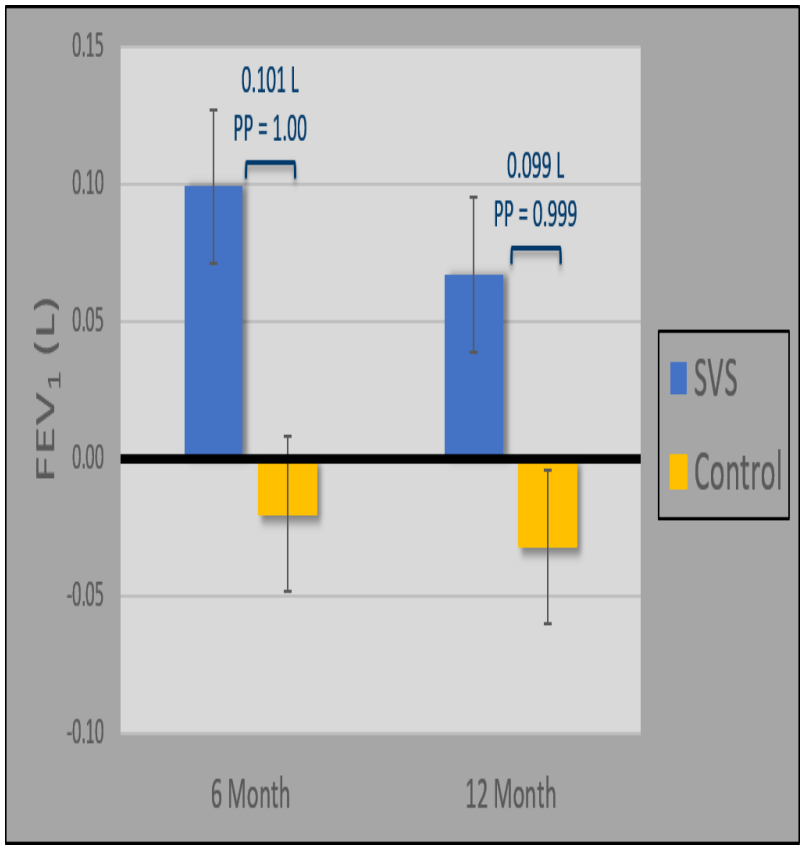


* p=0.053
** p=0.033

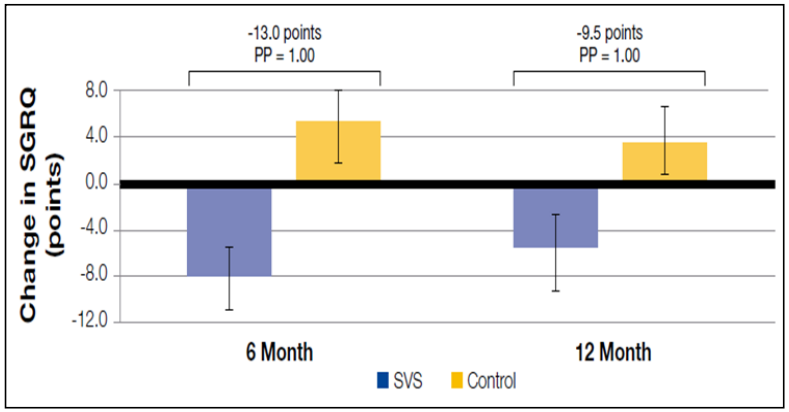
Criner, AJRCCM, 2018

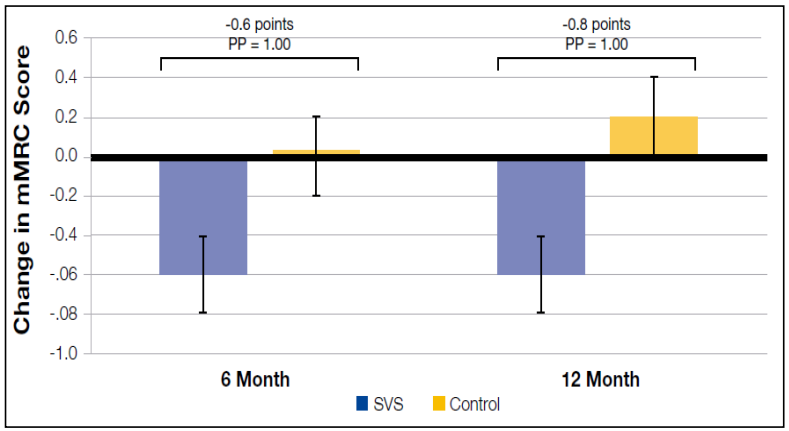
EMPROVE: Primary and Secondary Outcomes

Primary Outcome



Secondary Outcomes

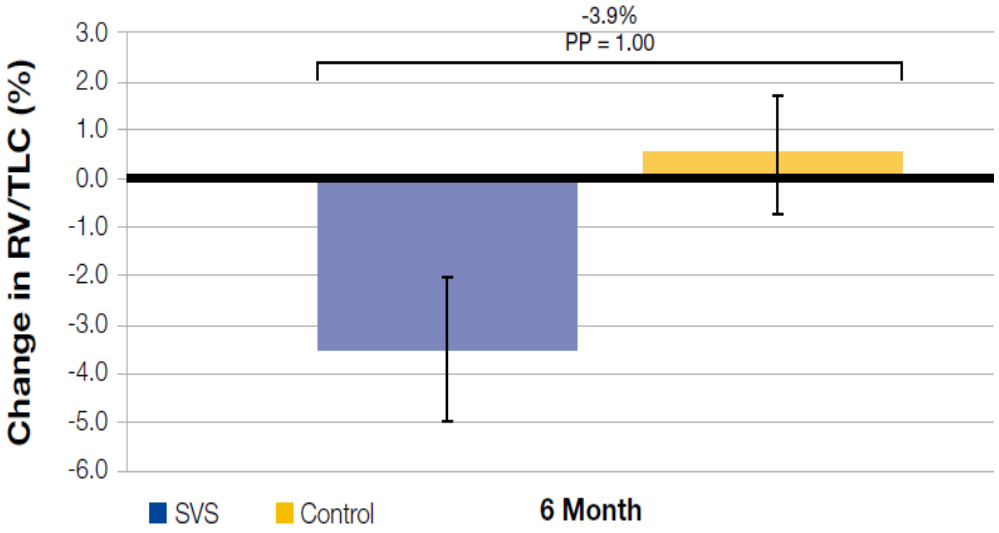




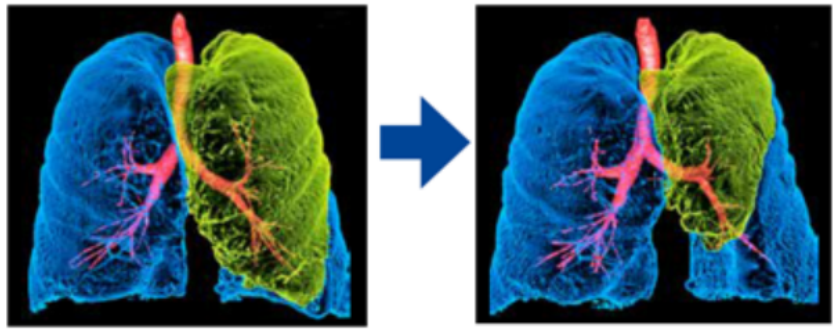
Criner, AJRCCM, 2019

EMPROVE Results

Secondary Endpoint: Reduced



Secondary Endpoint: Target Lobe Volume*



Pre-Treatment:
1.84 ± 0.6 L

Post-Treatment:
0.87 ± 0.9 L

53% REDUCTION
Difference: -0.974 L

95% BCI: -1.119, -0.829 PP: 1.0000

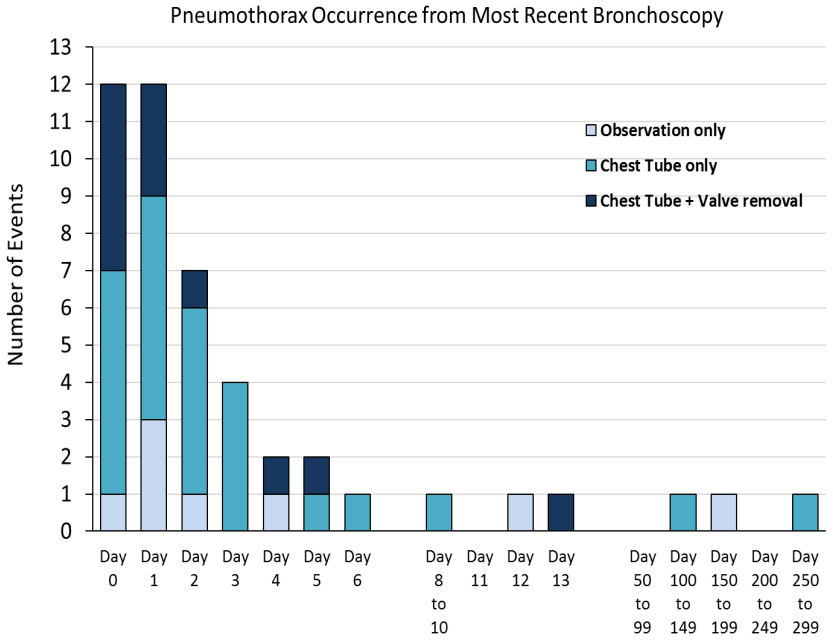
Atelectasis	
Complete (≥99% TLVR)	40/102(39%)
Substantial (≥50% TLVR)	51/102 (50%)
MCID Responder (≥350ml TLVR)	76/102 (75%)

* Statistically significant at 6 months. Only measured at 6 months.
Mean ±95% Bayesian Credible Interval PP = Posterior Probability

Criner, AJRCCM, 2019

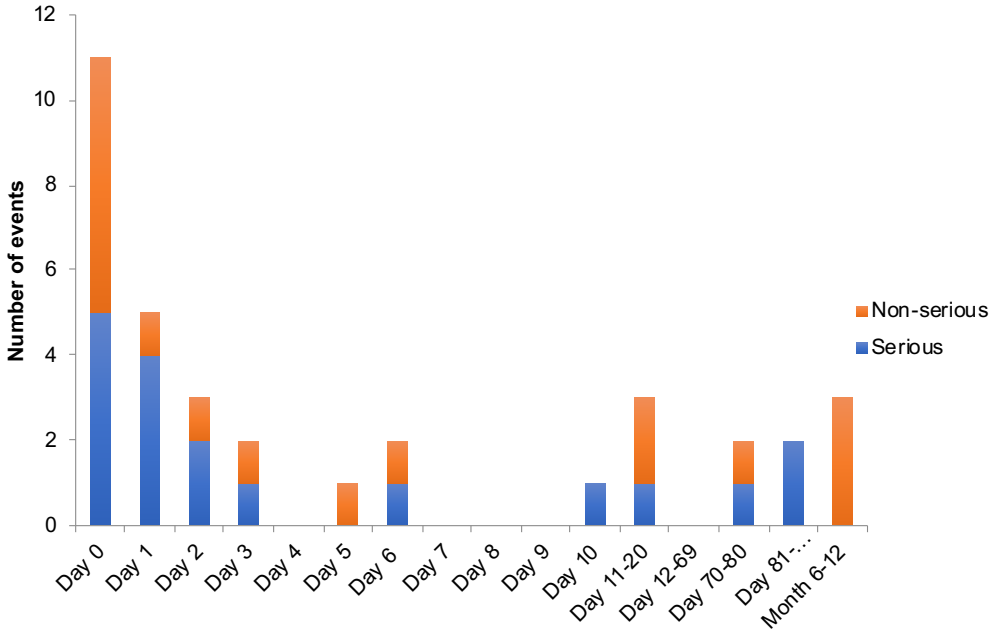
Pneumothorax Post BLVR in LIBERATE and EMPROVE

LIBERATE



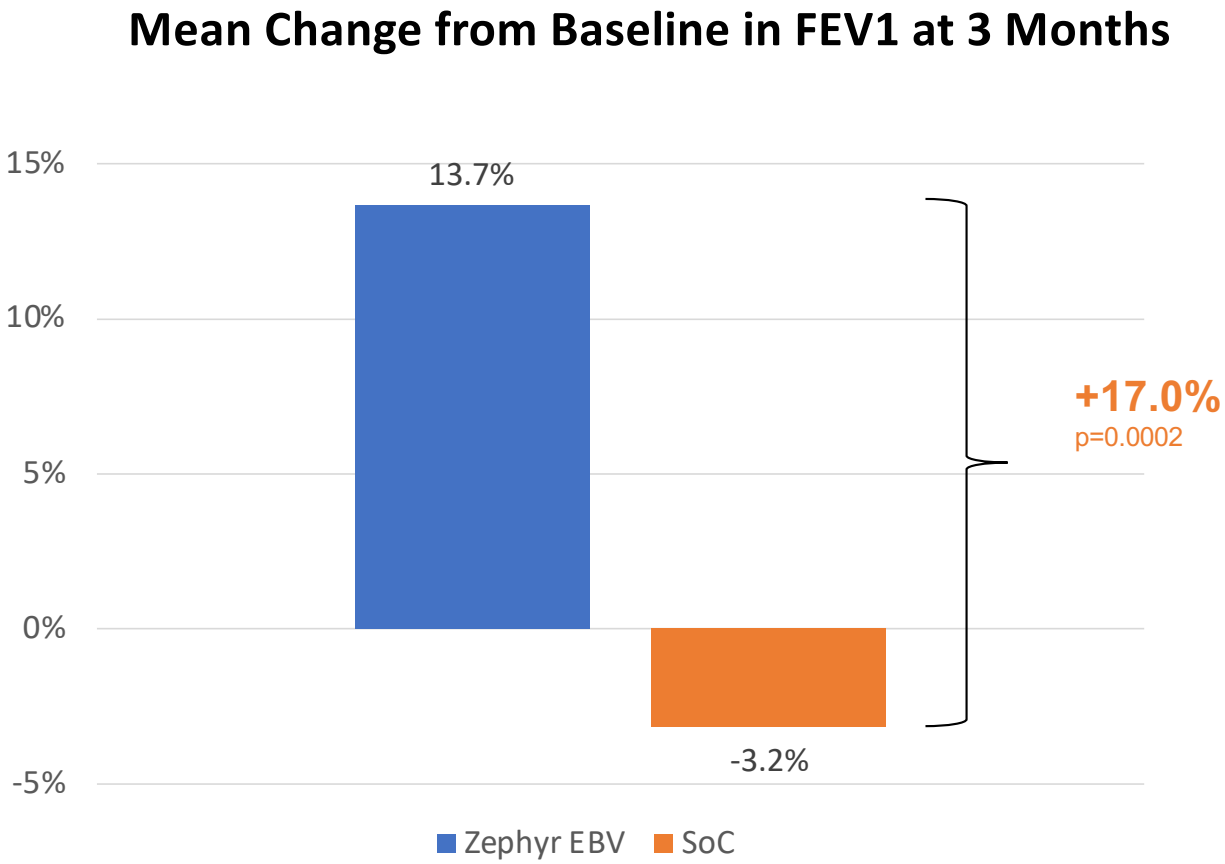
Criner, AJRCCM, 2018

EMPROVE



Criner, AJRCCM, 2019

Homogenous Emphysema: IMPACT - Primary Outcome



Valipour A et al, AJRCCM 2016. 194: 1073–1082

Mortality in LIBERATE and EMPROVE

LIBERATE

Treatment Period Day of Procedure/Randomization to 45 Days		Longer-Term Period 45 Days from the Study Procedure/Randomization until 12-month Visit Date	
EBV (N=128)	SoC (N=62)	EBV (N=122)	SoC (N=62)
4 (3.1%)[a]	0 (0.0%)	1 (0.8%)	1 (1.6%)

EMPROVE

Treatment Period Day of Procedure/Randomization to 6 months		Longer-Term Period 6 months from the Study Procedure/Randomization until 12-month Visit Date	
EBV (N=113)	SoC (N=59)	EBV (N=103)	SoC (N=47)
6 (5.3%)[a]	1 (1.7%)	4 (3.9%)	3 (6.4%)

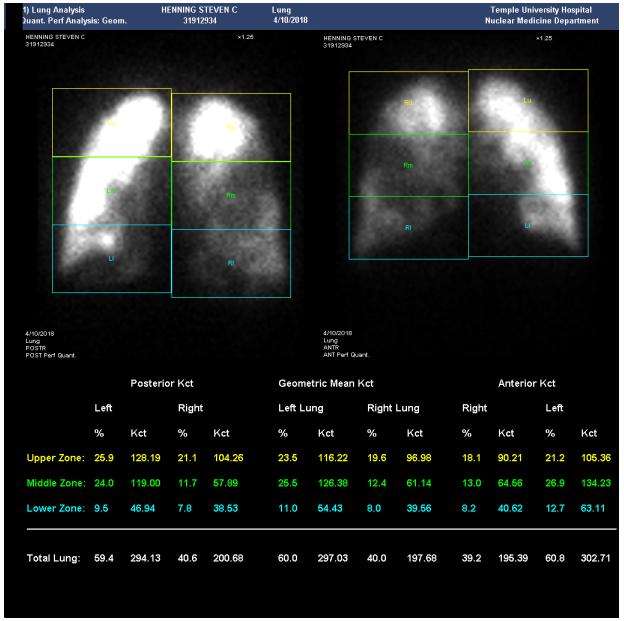
[A] 2 deaths occurred before protocol changed to require 5 days hospitalization post procedure; 3 deaths not treated in most diseased lobe

[a] 1 event device related by adjudication

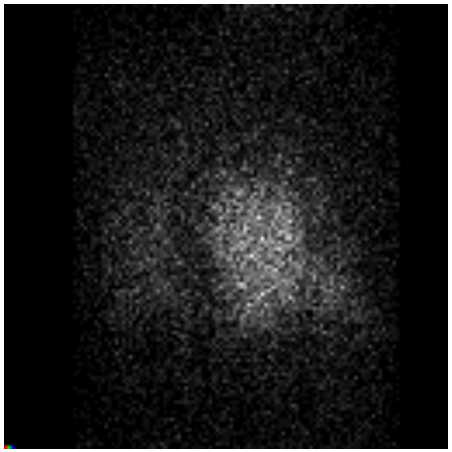
Patient Case

Medical History	Baseline
Gender (M/F)	Male
Age	63
BMI	31.19 kg/m2
Pack years	35
Stopped smoking since, yrs	2011
Exacerbations last 12 mo requiring hosp	2 mild
Medical History (highlights only)	COPD, Gold IV
mMRC	Grade 4
Other significant findings	Treated prostate ca
Did rehab/physically active	yes
Flu/pneumoccocal vaccines	yes

Lung Function	Baseline
FEV_1, %pred	21 %
TLC %	138 %
RV, %pred*	281 %
6 MWT	390 M
PaCO2	37mm Hg
PO2	75mm Hg

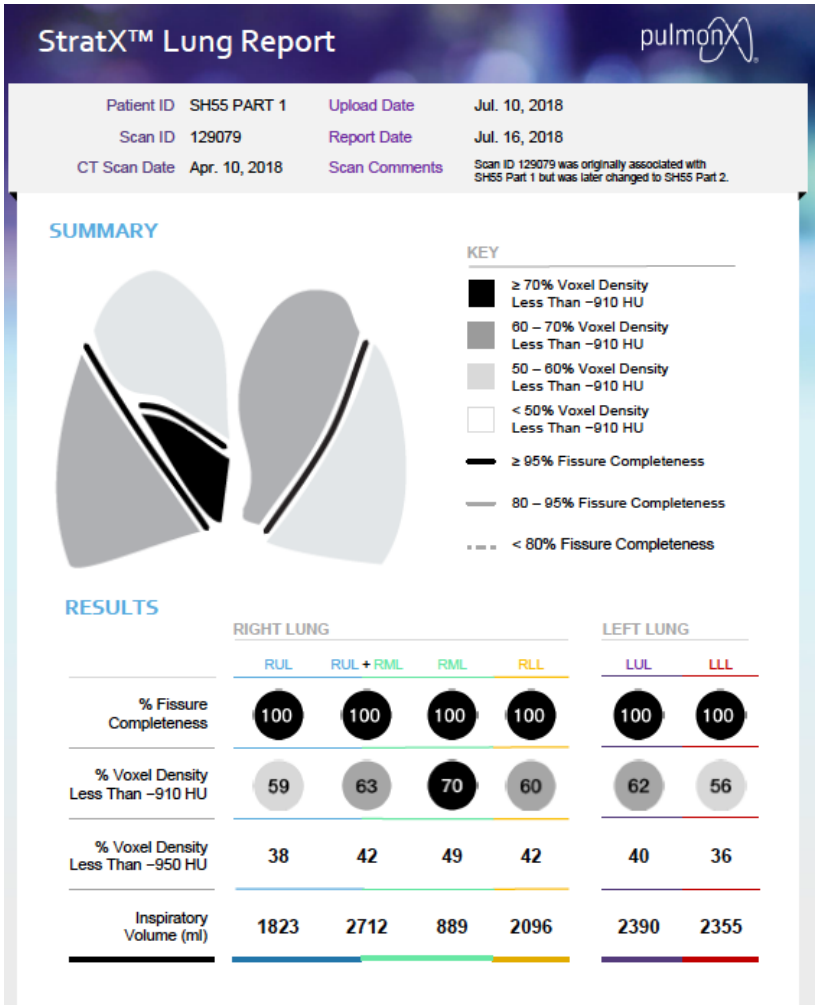


V/RPO



Further Assessment

RUL is CV-



StratX™ Lung Report

pulmonX

Patient ID	SH55 PART 1	Upload Date	Jul. 10, 2018
Scan ID	129079	Report Date	Jul. 16, 2018
CT Scan Date	Apr. 10, 2018	Scan Comments	Scan ID 129079 was originally associated with SH55 Part 1 but was later changed to SH55 Part 2.

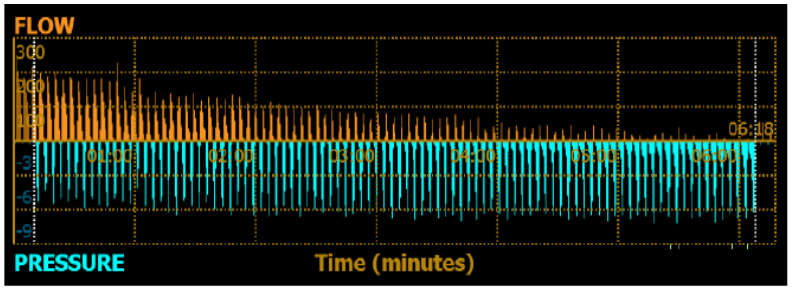
SUMMARY

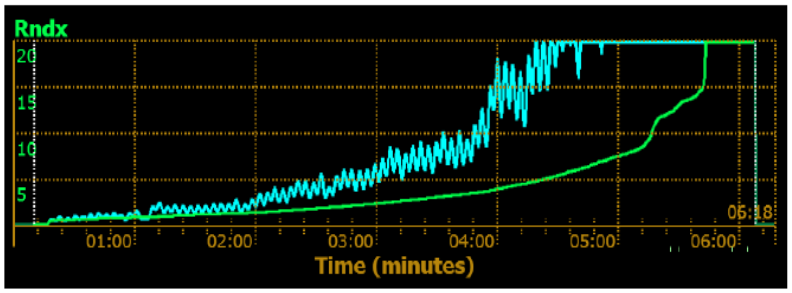
KEY

- ≥ 70% Voxel Density Less Than −910 HU
- 60 – 70% Voxel Density Less Than −910 HU
- 50 – 60% Voxel Density Less Than −910 HU
- < 50% Voxel Density Less Than −910 HU
- ≥ 95% Fissure Completeness
- 80 – 95% Fissure Completeness
- < 80% Fissure Completeness

RESULTS

	RIGHT LUNG				LEFT LUNG	
	RUL	RUL + RML	RML	RLL	LUL	LLL
% Fissure Completeness	100	100	100	100	100	100
% Voxel Density Less Than −910 HU	59	63	70	60	62	56
% Voxel Density Less Than −950 HU	38	42	49	42	40	36
Inspiratory Volume (ml)	1823	2712	889	2096	2390	2355

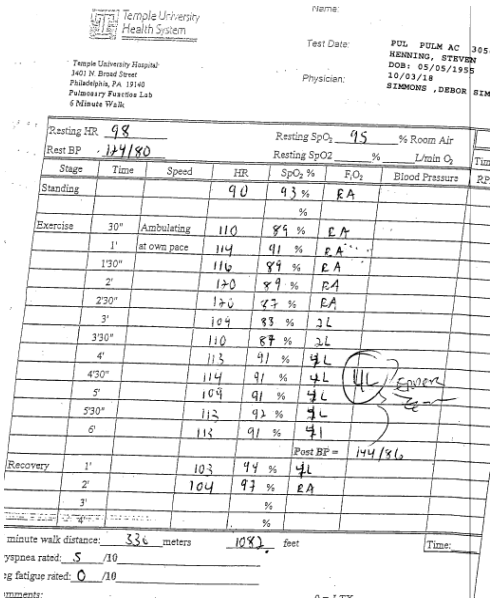




- Bilateral complete fissures
- RTG lung > left lung emphysema burden
- RLL volume 2096
- RML volume 889
- RML + RLL 2985

6-month Follow-up

	Baseline	RML	RML+ RLL
FVC Post	3.21	3.13	4.31
FVC %PostPred	64	62	86
FEV1 Post	1.03	0.99	1.26
TLC Post	9.71	9.47	8.77
TLC %Postpred	131	128	118
RV Post	6.50	6.34	4.42
RV % Post Pred	269	262	183
DLCO Post	14.4	13.2	15.0



Temple University Health System

Name:

Test Date:

Physician:

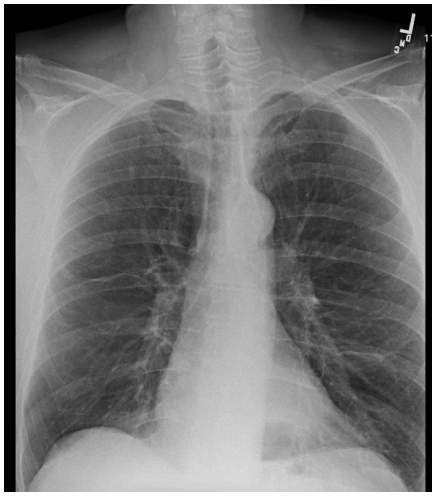
PUL PULM AC 305
HENNING, STEVEN
DOB: 05/05/1955
10/03/18
SIMMONS ,DEBOR SIM

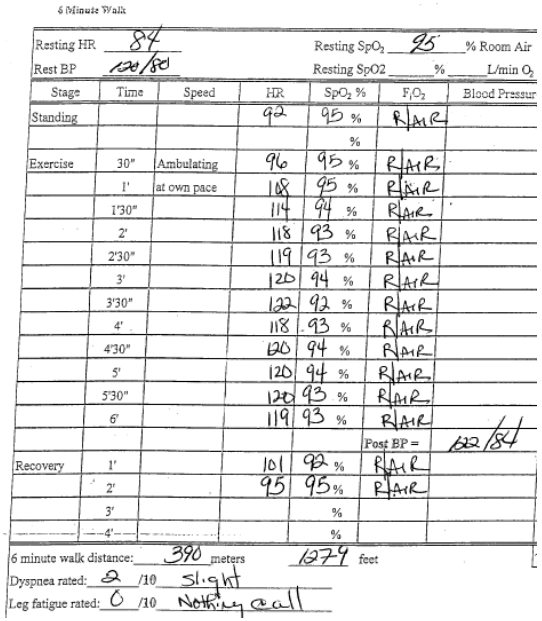
Temple University Hospital
3401 N. Broad Street
Philadelphia, PA 19140
Pulmonary Function Lab
6 Minute Walk

Resting HR 98 Resting SpO_2 95 % Room Air
Rest BP 124/80 Resting SpO2 ____ % ____ L/min O_2

Stage	Time	Speed	HR	SpO_2 %	F_iO_2	Blood Pressure
Standing			90	93 %	RA	
				%		
Exercise	30"	Ambulating	110	89 %	RA	
	1'	at own pace	114	91 %	RA	
	1'30"		116	89 %	RA	
	2'		120	89 %	RA	
	2'30"		126	87 %	RA	
	3'		104	83 %	2L	
	3'30"		110	87 %	2L	
	4'		113	91 %	4L	
	4'30"		114	91 %	4L	
	5'		109	91 %	4L	
	5'30"		112	92 %	4L	
	6'		113	91 %	4L	
					Post BP =	144/86
Recovery	1'		103	94 %	4L	
	2'		104	97 %	RA	
	3'			%		
	4'			%		

6 minute walk distance: 336 meters 1082 feet Time:
Dyspnea rated: 5 /10
Leg fatigue rated: 0 /10



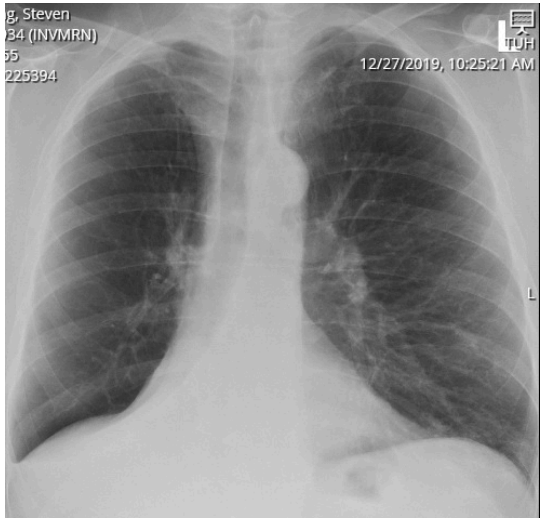


6 Minute Walk

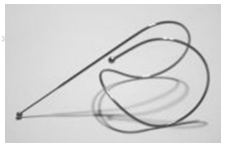
Resting HR 84 Resting SpO_2 95 % Room Air
Rest BP 120/80 Resting SpO2 ____ % ____ L/min O_2

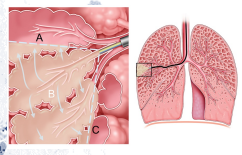
Stage	Time	Speed	HR	SpO_2 %	F_iO_2	Blood Pressur
Standing			92	95 %	R/AIR	
				%		
Exercise	30"	Ambulating	96	95 %	R/AIR	
	1'	at own pace	18	95 %	R/AIR	
	1'30"		114	94 %	R/AIR	
	2'		118	93 %	R/AIR	
	2'30"		119	93 %	R/AIR	
	3'		120	94 %	R/AIR	
	3'30"		122	92 %	R/AIR	
	4'		118	93 %	R/AIR	
	4'30"		120	94 %	R/AIR	
	5'		120	94 %	R/AIR	
	5'30"		120	93 %	R/AIR	
	6'		119	93 %	R/AIR	
					Post BP =	122/84
Recovery	1'		101	92 %	R/AIR	
	2'		95	95 %	R/AIR	
	3'			%		
	4'			%		

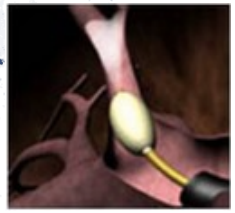
6 minute walk distance: 390 meters 1274 feet
Dyspnea rated: 2 /10 Slight
Leg fatigue rated: 0 /10 Nothing at all



What can be done if there are Incomplete Fissures or CV+ status on Chartis Assessment







CV+ by Chartis or FI< 90% by QCT

- Lung Coils (ELEVATE trial, OUS)*
- Flowables- tissue adhesives and sclerosing agents (Phase II trials, OUS)
- Bronchoscopic Thermal Vapor Ablation (Limited availability OUS, Phase II trial homogenous disease)*

* GOLD Report 2020, Evidence B

Research

Original Investigation

Effect of Endobronchial Coils vs Usual Care on Exercise Tolerance in Patients With Severe Emphysema

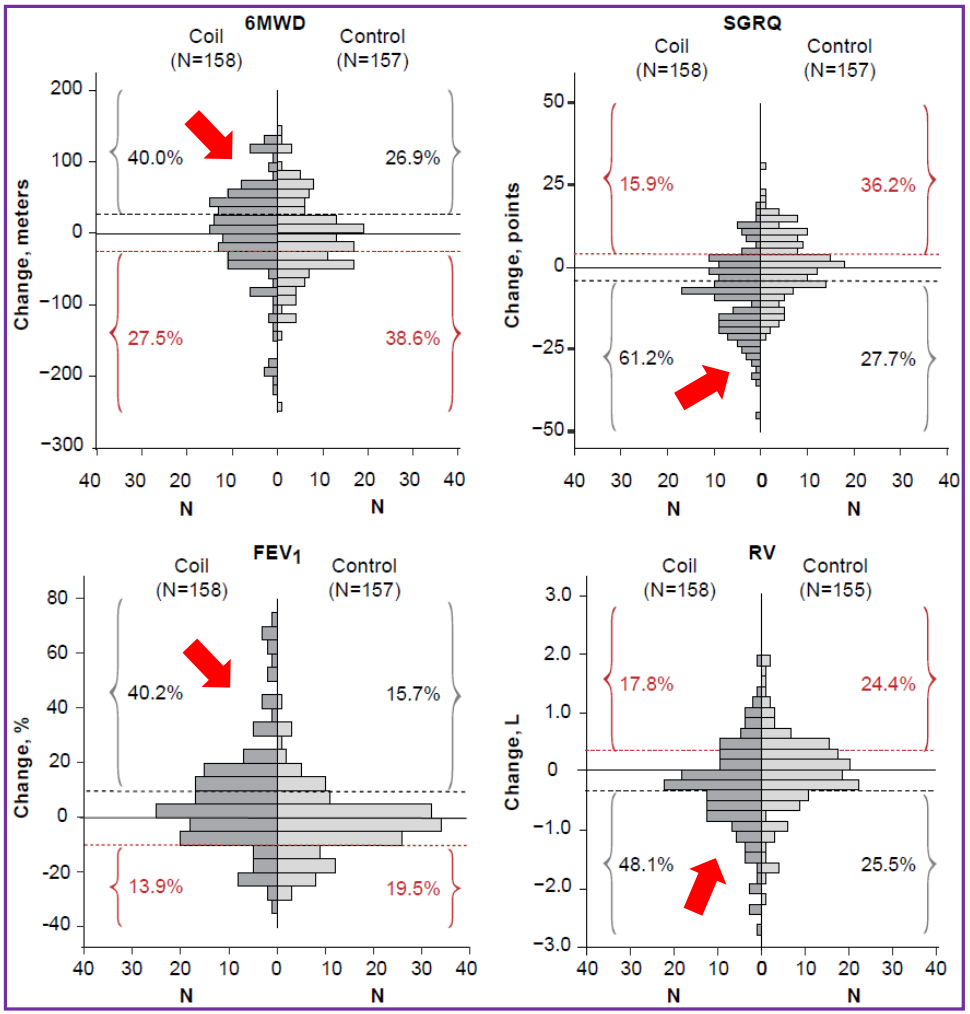
The RENEW Randomized Clinical Trial

Frank C. Sciurba, MD; Gerard J. Criner, MD; Charlie Strange, MD; Pallav L. Shah, MD; Gaetane Michaud, MD; Timothy A. Connolly, MD; Gaëtan Deslée, MD; William P. Tillis, MD; Antoine Delage, MD; Charles-Hugo Marquette, MD, PhD; Ganesh Krishna, MD; Ravi Kalhan, MD; J. Scott Ferguson, MD; Michael Jantz, MD; Fabien Maldonado, MD; Robert McKenna, MD; Adnan Majid, MD; Navdeep Rai, MD; Steven Gay, MD; Mark T. Dransfield, MD; Luis Angel, MD; Roger Maxfield, MD; Felix J. F. Herth, MD; Momen M. Wahidi, MD; Atul Mehta, MD; Dirk-Jan Slebos, MD, PhD; for the RENEW Study Research Group

	Tx Diff.	p
6m Walk Distance	14.6* (0.4, ∞)	0.015**
FEV1%	7.0 (3.4, ∞)	<0.001
RV (L)	-0.31 (-∞, -0.11)	0.001
SGRQ Total Score	-8.9 (-∞, -6.3)	<0.001

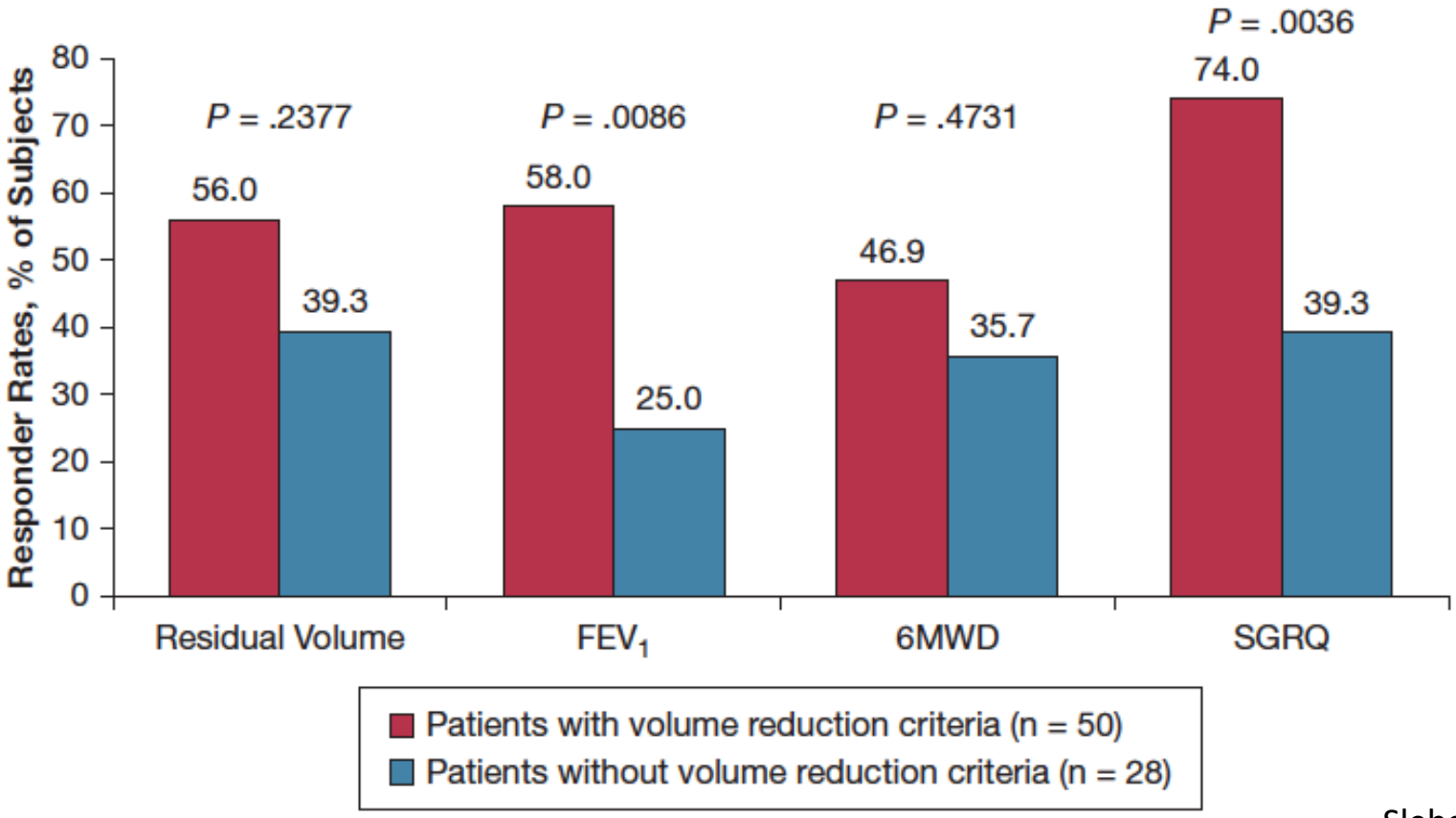
~ 80% Homogenous Emphysema

N=315/ 1:1



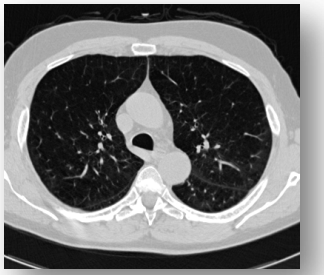
Sciurba, JAMA, 2016

Predictors of Response to Coil Therapy: RV> 200% predicted, LAA> 20%, no significant Airways disease



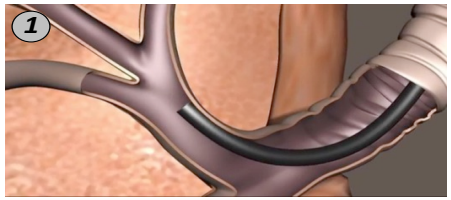
Slebos Chest 2019

Vapor Ablation of Emphysema - BTVA

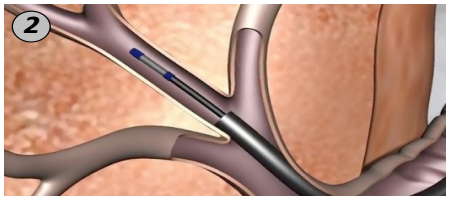


HRCT

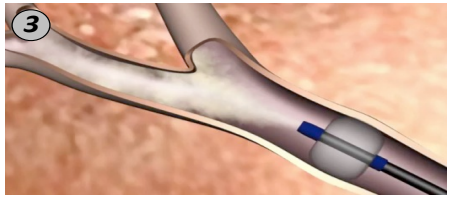
Vapor Generator, Catheter & Treatment plan



Bronchoscope inserted into target segment airway



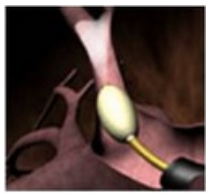
InterVapor™ Catheter positioned into target segment airway



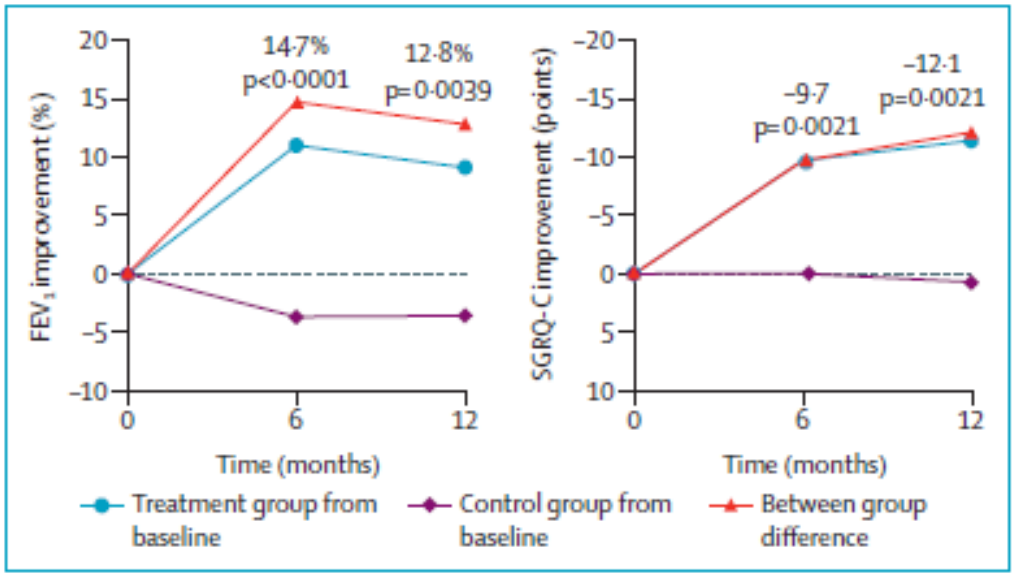
Occlusion balloon inflated and thermal vapour delivered

Thermal vapour delivery time based on *IP3™*: 3 to 10 seconds

- HRCT used to determine *most diseased segments* & treatment plan
- Vapor delivered to most diseased hyperinflated *segments*
- Diseased hyperinflated tissue reduced via reparative process
- LVR occurs over 6 wks (mitigating risk of pneumothorax) independent of Collateral Ventilation (CV)
- Allows sequential treatments for optimized outcomes based on individual disease distribution
- No foreign body left in patient



Thermal Vapor Ablation: Step Up Trial



N=70 2:1

	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.

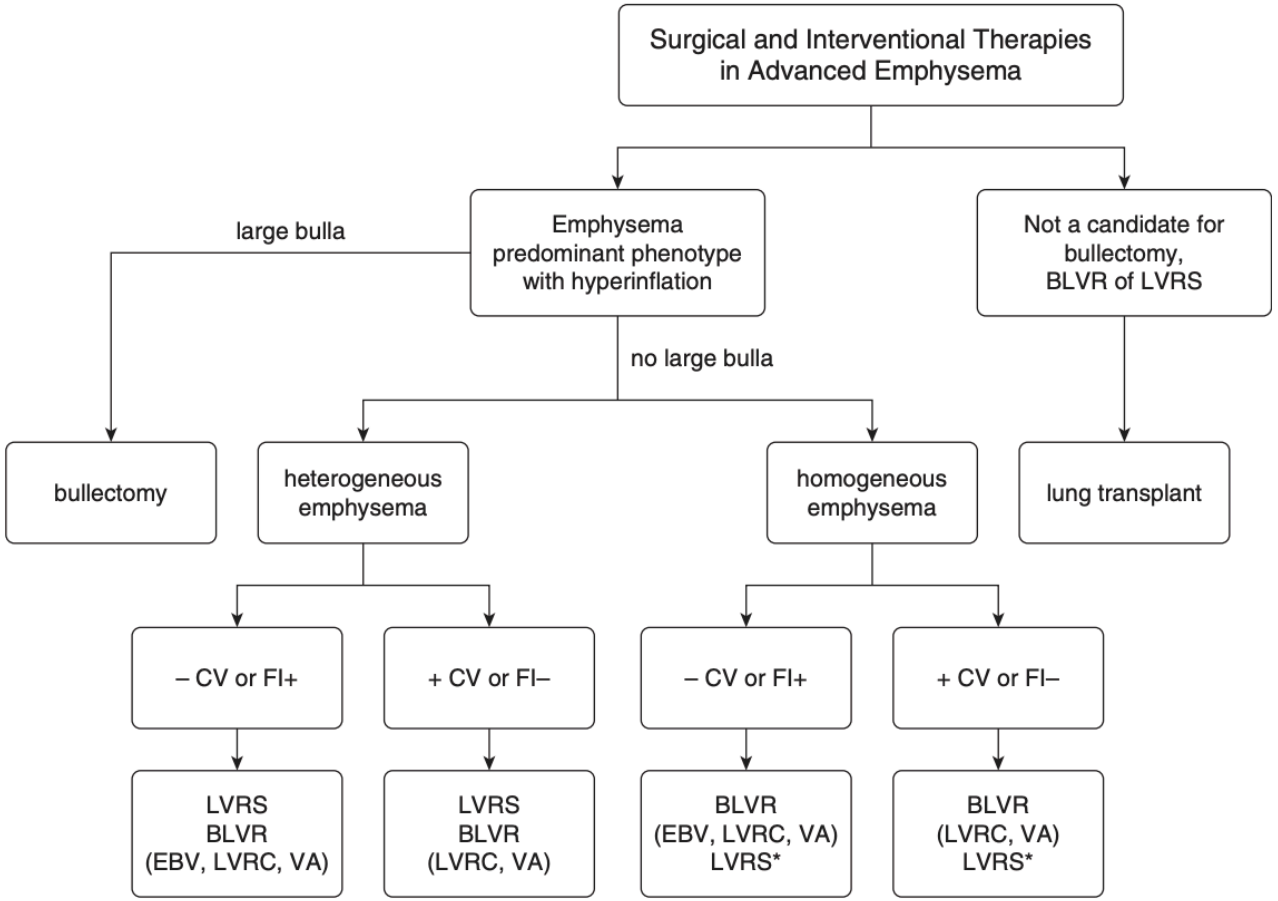
Table 6: **Serious adverse events and hospital admissions**

Herth Lancet Respir Med 2016; 4: 185–93
Shah Lancet Respir Med 2016; 4: e44 –e45

Where are we with BLVR using EBV?

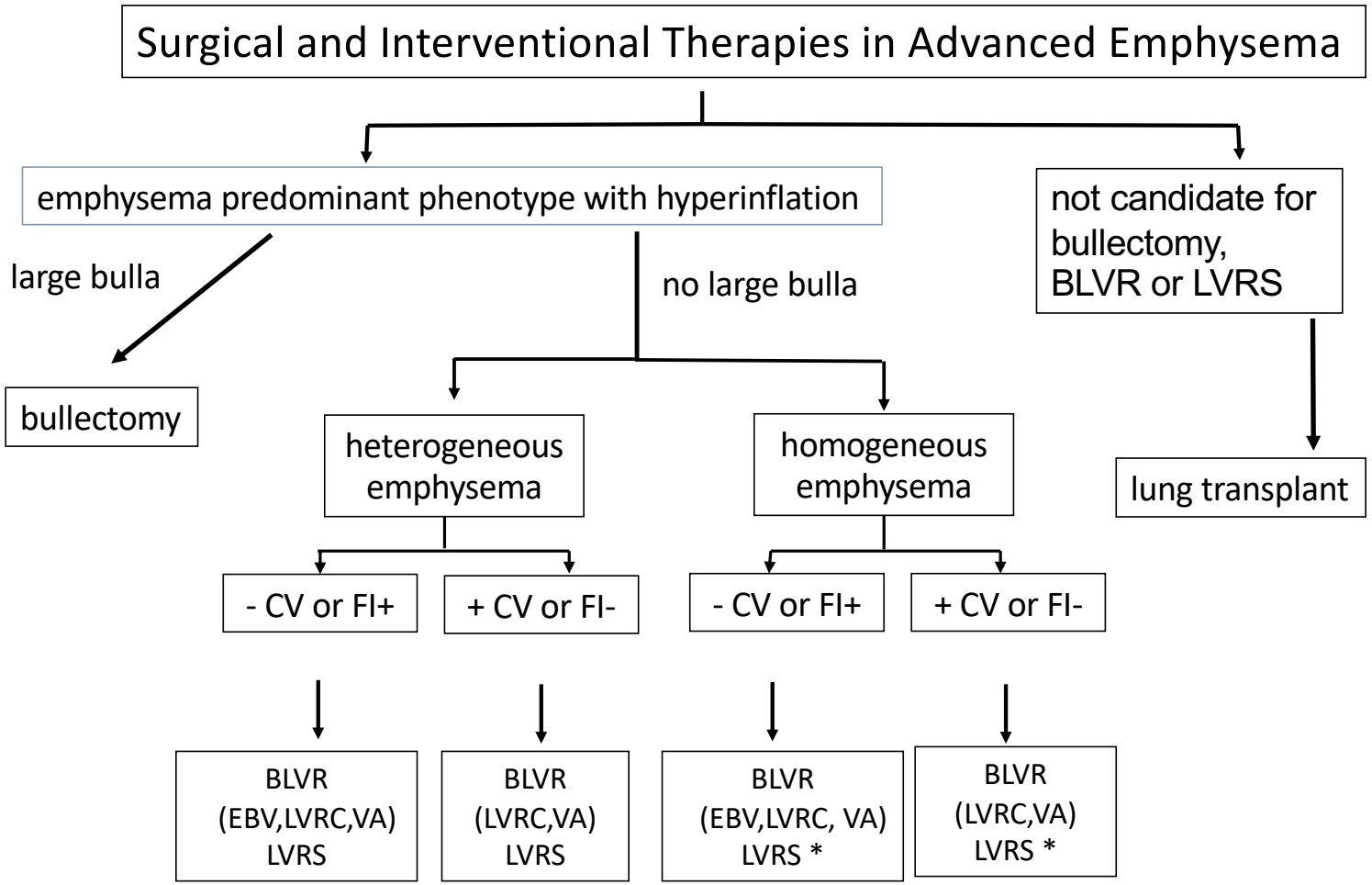
- In patients with advanced emphysema and hyperinflation selected for fissure integrity (FI) or lack of collateral ventilation (CV), BLVR with EBV and total lobar occlusion can ***achieve clinically significant and durable improvements in lung function, dyspnea, exercise tolerance and quality of life. (GOLD Report 2020: Evidence A)***
- Future work needs to:
  - ***Refine patient selection to improve outcomes***
  - ***Reduce complications***
  - ***Refine procedural performance***

Overview of Surgical and Interventional Therapies for Emphysema



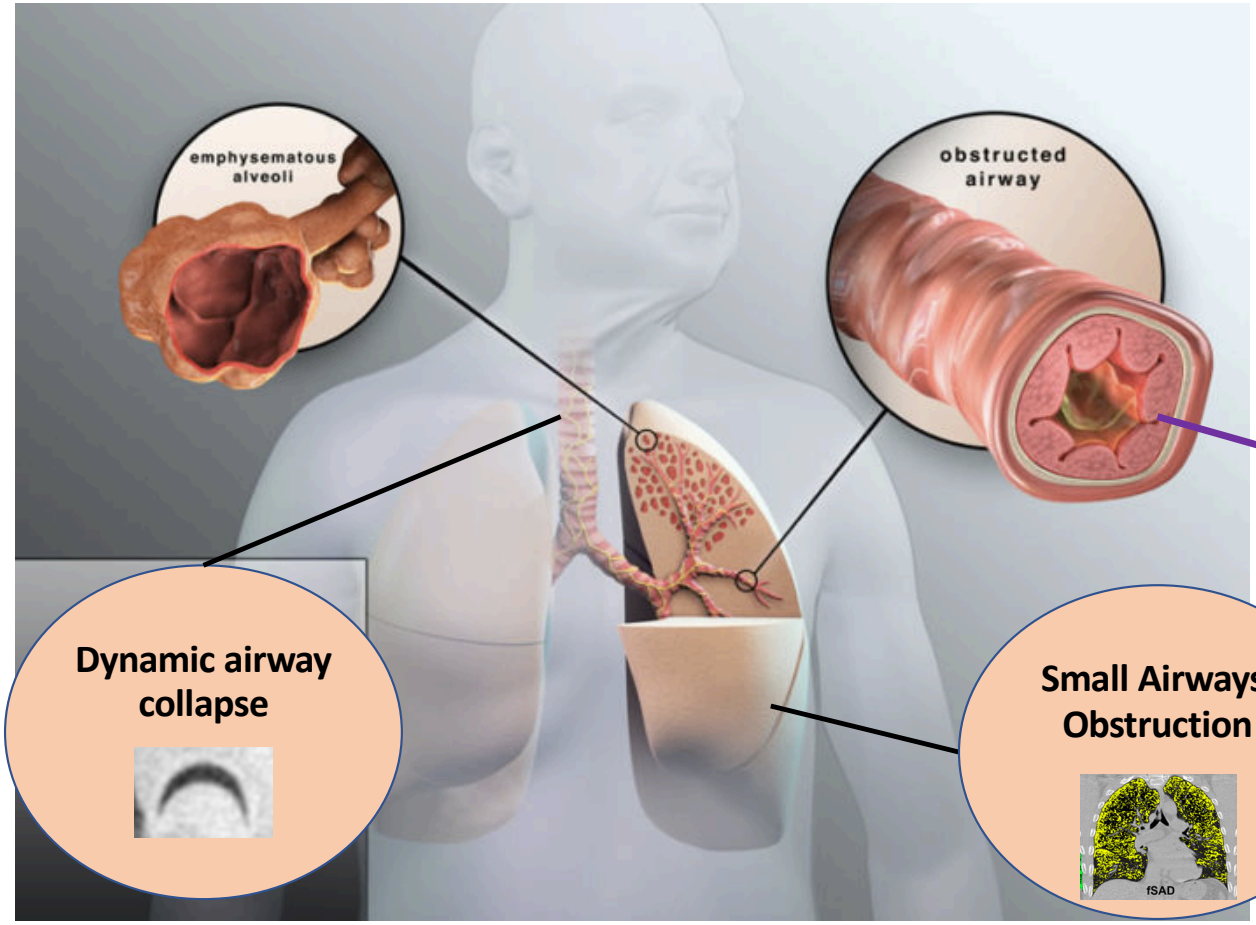
Criner, AJRCCM, 2020

Note: not all therapies are clinically available in all countries. Long term BLVR outcomes or direct comparisons to LVRS are unknown.



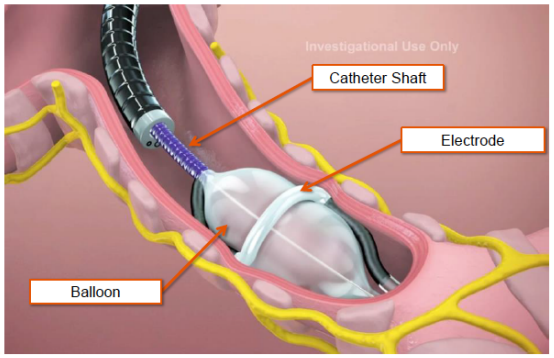
Definition of abbreviations: CV, collateral ventilation measure by Chartis; FI + fissure integrity > 90% by HRCT; FI-, fissure integrity < 90% by HRCT; BLVR, Bronchoscopic Lung Volume Reduction, EBV, Endobronchial Valve; VA, Vapor Ablation; LVRC, Lung Volume Reduction Coil; LVRS, Lung Volume Reduction Surgery. Modified from Vogelmeier, AJRCCM, 2017

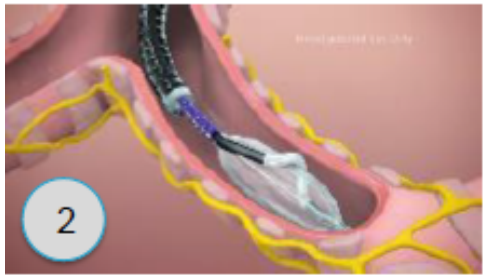
Range of Abnormalities that May Cause Hyperinflation in Patients with Chronic Airflow Obstruction/Emphysema



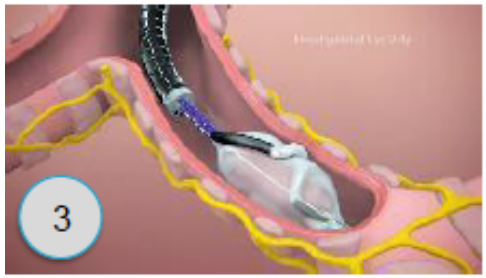
TLD Device and Procedure

dNerva™ Dual Cooled Catheter

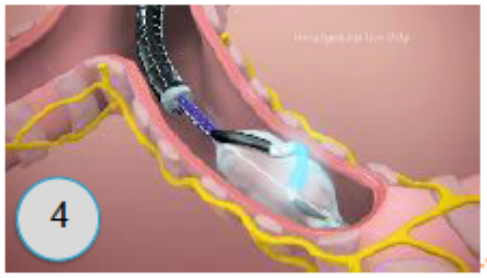




Inflate



Confirm



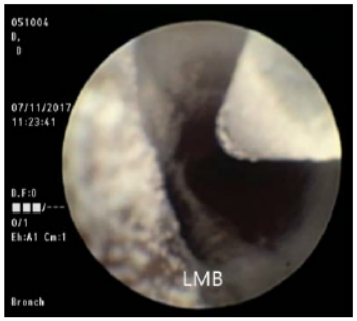
Activate

RejuvenAir® Chronic Bronchitis Study

A lifetime of specialist care

Immediately before spray

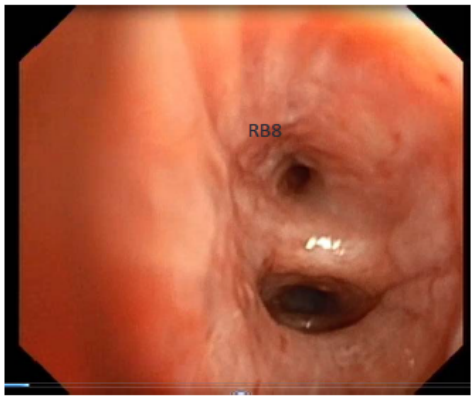
Metered Cryospray Frost



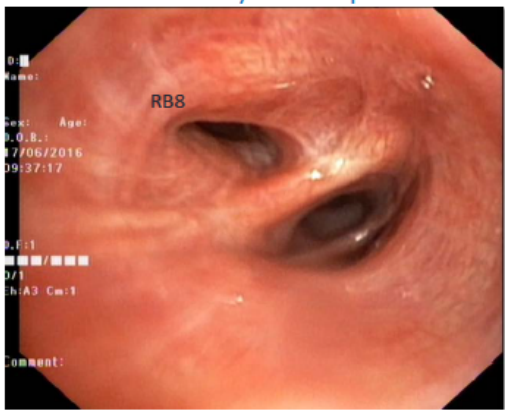
Immediately after spray

Tissue shows no trauma immediately after spray

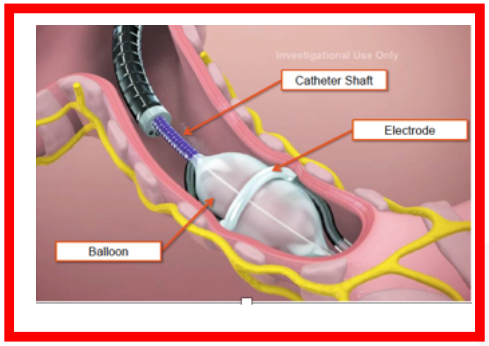
Before Treatment



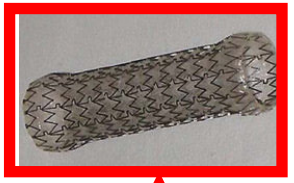
60 day follow-up



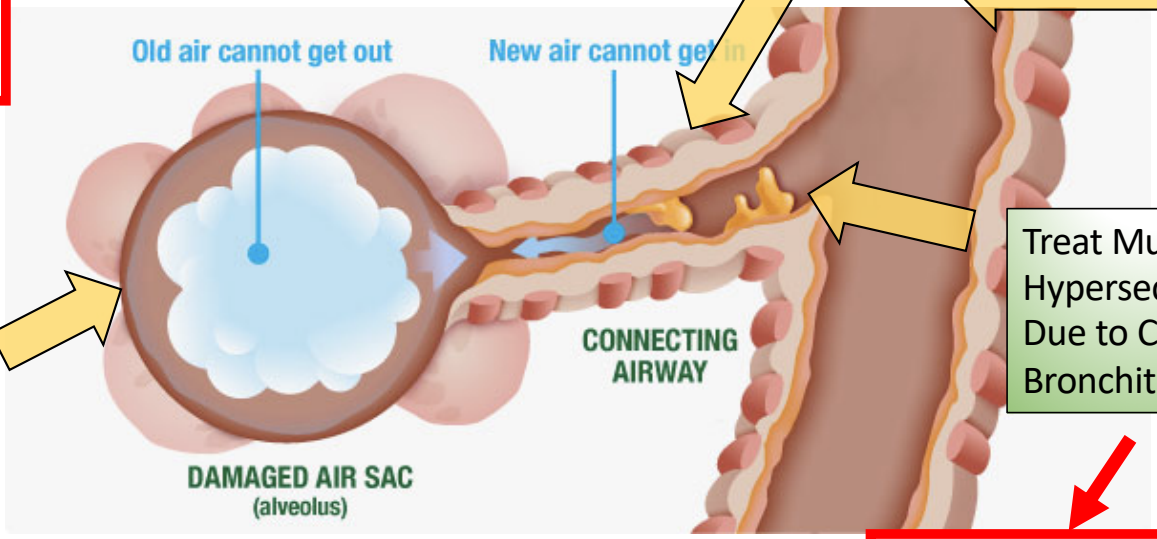
New Targets for Treatment



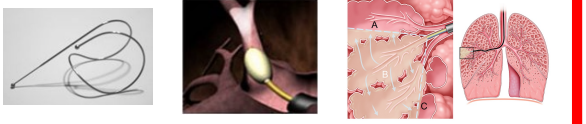
Alleviate Airway Bronchoconstriction



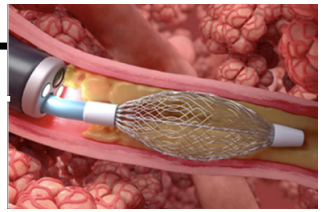
Dynamic airway collapse

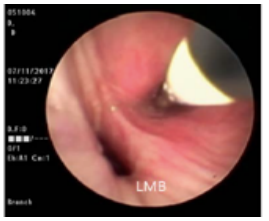


Reduce Hyperinflation Caused by Emphysema or Small Airways Obstruction



Treat Mucus Hypersecretion Due to Chronic Bronchitis





Prevent Future Exacerbations