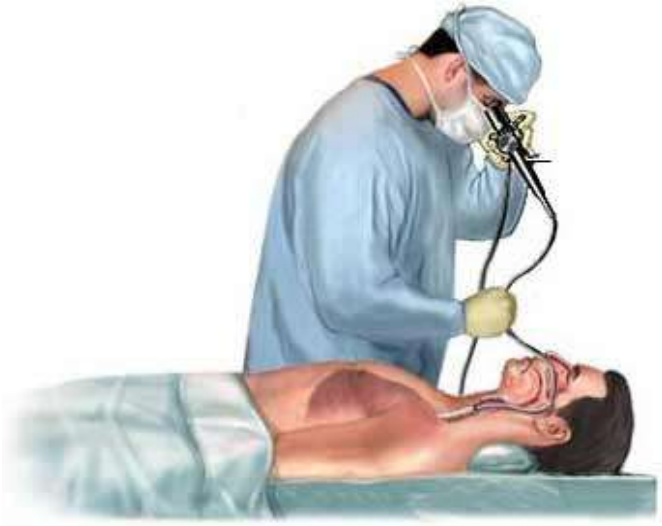


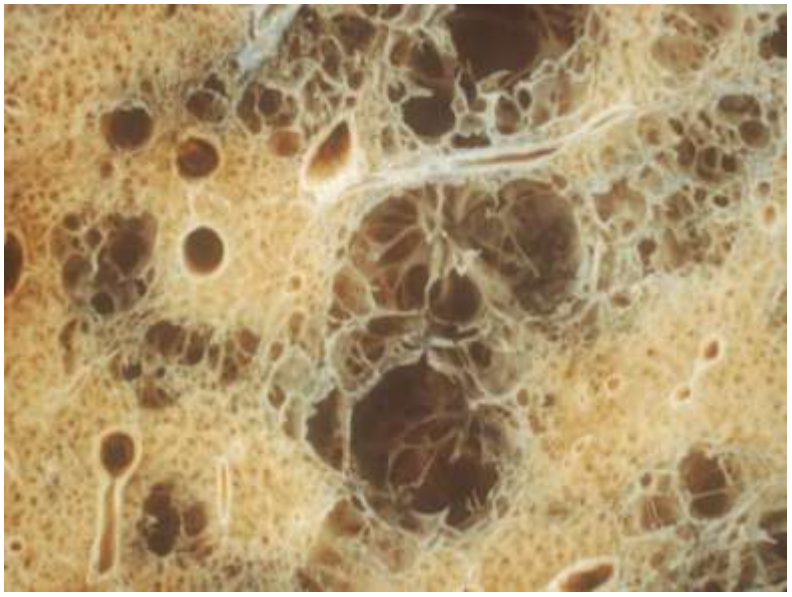
Tractament endoscòpic de l'emfisema pulmonar

Carles Agustí

Servei de Pneumologia
Institut del Tòrax
Hospital Clínic Barcelona

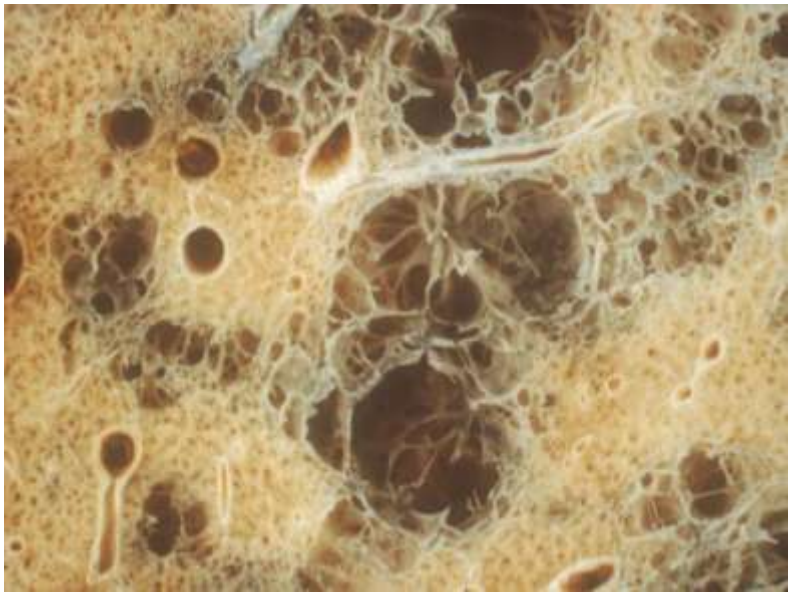
Emfisema pulmonar

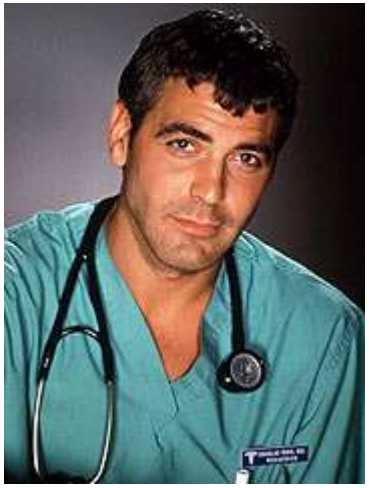
El engrandiment permanent dels espais aeris distals als bronquíols terminals, a causa de la destrucció de la paret alveolar



"El treball d'un metge (pneumòleg, especialment) consisteix en entretenir al pacient mentre actua la naturalesa".

Voltaire





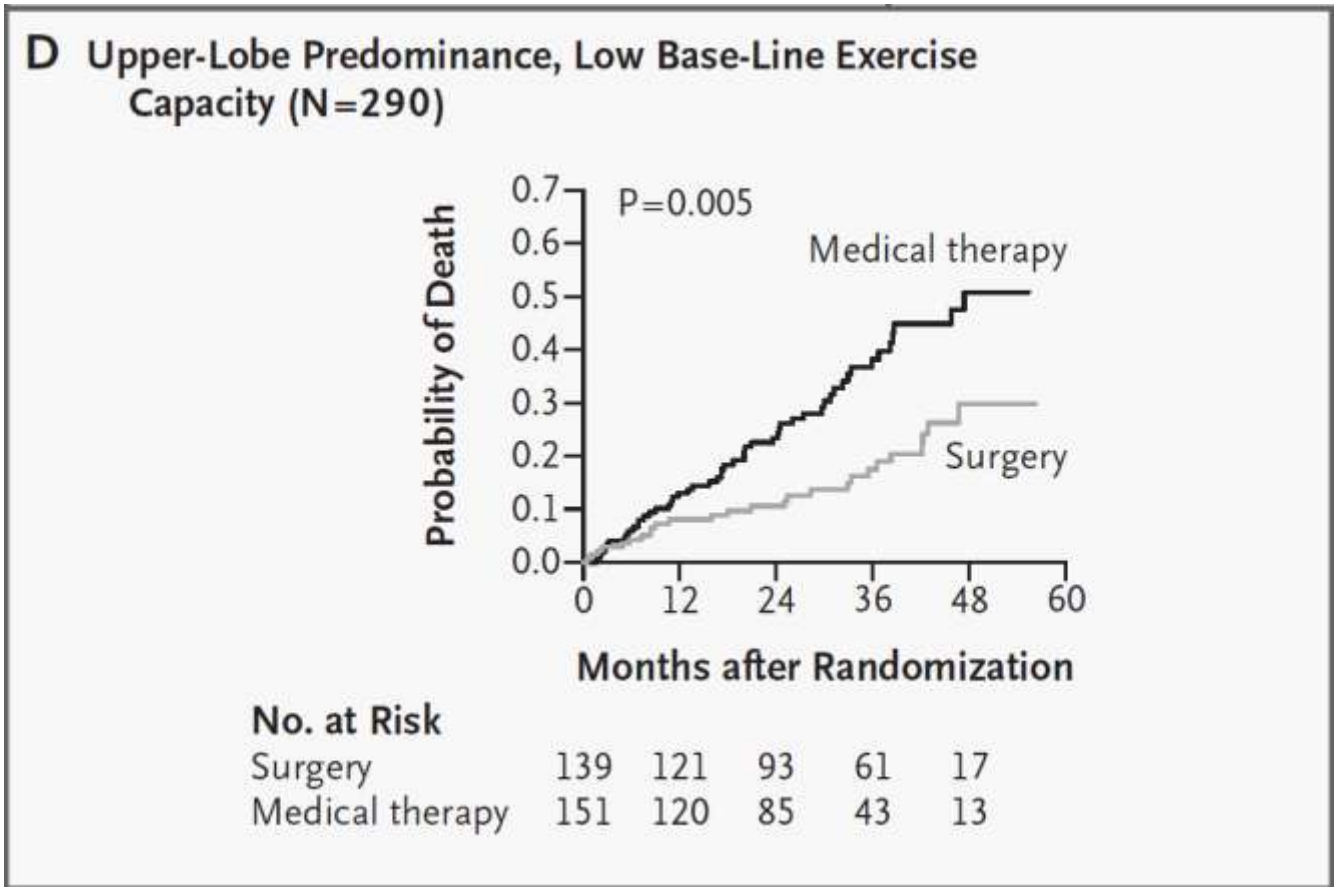
"El buen cirujano opera temprano…"

Anónimo

Encara que a priori és difícil creure que una malaltia caracteritzada per una pèrdua de parènquima pulmonar es pot tractar mitjançant resecció de pulmó...

Emphysema & Lung Volume Reduction: Results of NETT

(18.7% vs 33.8%)



N Engl J Med 2003;348:2059

Situació LVRS post-NETT

- Procediment eficaç (mortalitat, símptomes, PFRs).
- Grup molt seleccionat de candidats òptims.
- Morbi-mortalitat elevada.
- Costos elevats.

Interès per nous procediments:

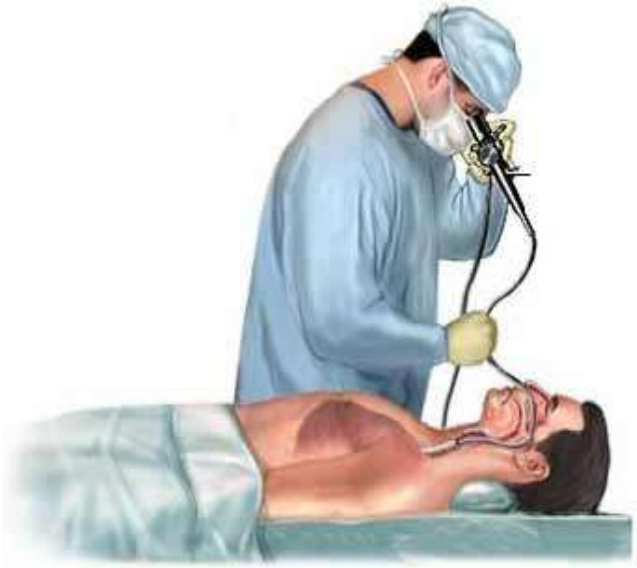
✓ Igual o més eficaços.

✓ Menor morbi-mortalitat.

✓ Indicat en major nombre de pacients.

✓ Més econòmics.

…”There is no pulmonary disease a little flexible bronchoscope can’t diagnose, cure or paliate”!



Bronchoscopy enthusiast

Bronchoscopic Emphysema Treatment

B.E.T.

Modalitats BET

- Vàlvules endobronquials
  - Zephyr (Pulmonx)

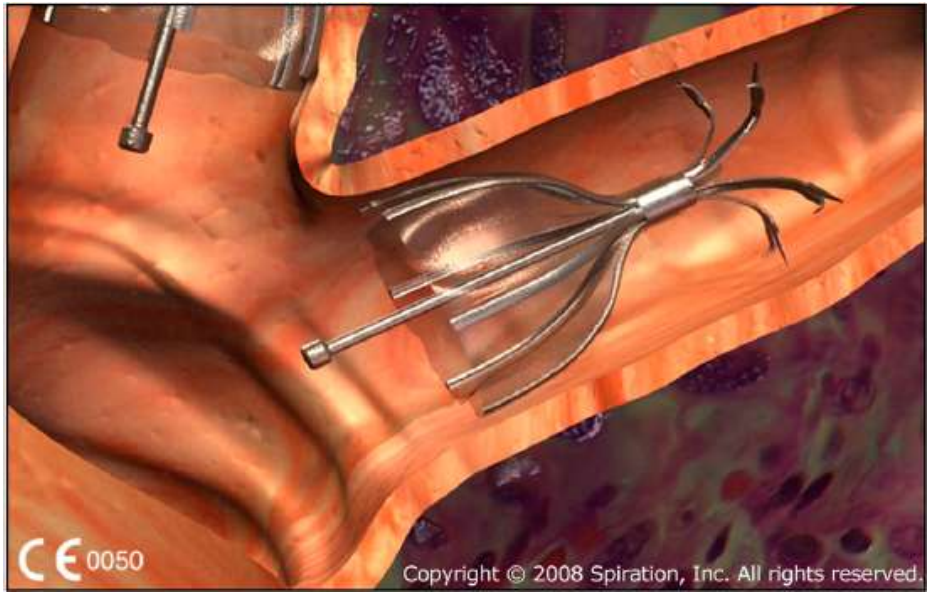
  - IBV (Spiration. Olympus)

- Substàncies biològiques/polimèriques (Aeriseal)

- Vaporització/lesió tèrmica

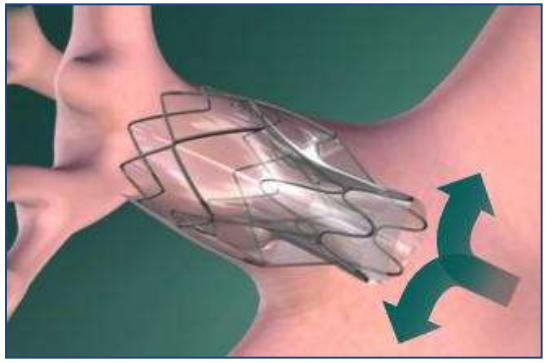
Vàlvules endobronquials

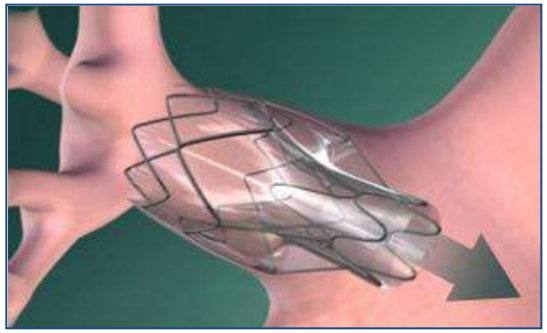
(Emphasys/Pulmonx]



IBV one-way valve (Spiration Inc.)

Endobronchial valve concept

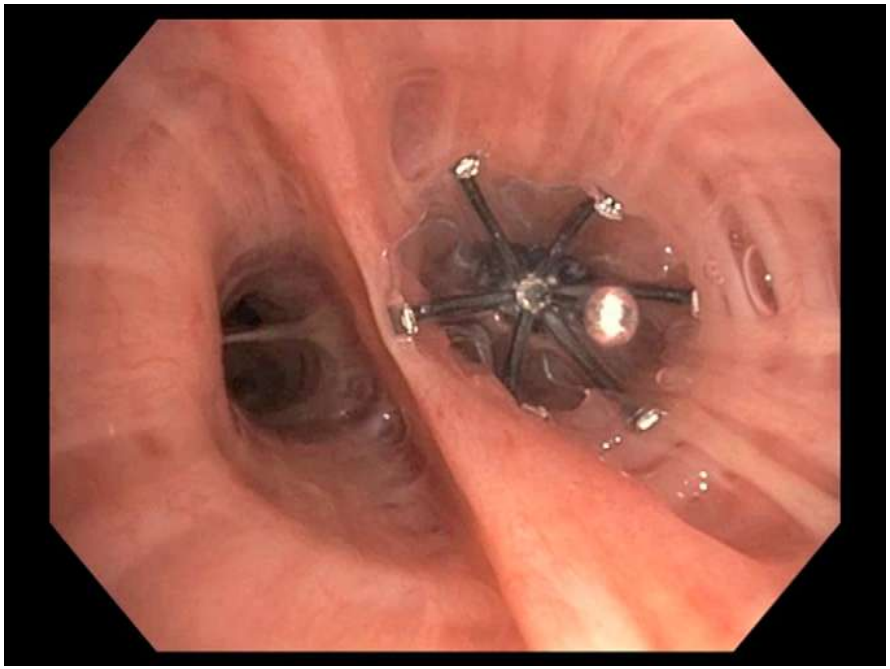




- Valve delivered through working channel of bronchoscope
- Removable with flexible graspers
- Prevents air entering diseased lung
- Allows trapped air and fluid to escape
- Intended to induce volume reduction/atelectasias

Endobronchial valves

Zephyr (Emphasys/Pulmonx)



IBV one-way valve (Spiration Inc.)

RCT: endobronchial valves

- **Sciurba FC, et al. NEJM 2010.**
- **Hertz et al. ERJ 2012.**
- **Ninane V. ERJ 2012.**

n	
Treatment	controls
362	183

Shah PL, et al. Thorax 2013;0:1–7. doi:10.1136/thoraxjnl-2013-203743

Endobronchial valves: Study design

- Multi-center
- Prospective/Randomized
- All subjects received optimal medical management prior to baseline
- CT Imaging core lab
- Key Entry Criteria similar to LVRS:
  - Severe disease determined by HRCT.
  - Pulmonary function tests: $15\% < FEV_1 < 45\%$; DLCO > 20%; RV: 150%

Safety Conclusions

- Procedure generally well tolerated with no increased risk of mortality .
- EBV Procedure resulted in relatively higher expected adverse event rates as compared to control group.
- Most complications early and minor.
- Complications tend to peak in 0-90 day period and decrease over time, approaching equivalence by 12 months.
- Ability to remove valves when clinically indicated.

RCT: endobronchial valves

Table 1 Percentage of patients experiencing adverse events at 90 days in the randomised clinical trials

	Treatment	Control
Death	0.8	0.6
COPD exacerbation with hospitalisation	9.2	4.8
COPD exacerbation without hospitalisation	10.5	15.7
Infection	1.2	0
Respiratory failure	2.2	0.7
Pneumonia distal to valve	1.9	–
Pneumonia other lobe	2.8	2.0
Haemoptysis: massive	0.6	0
Pneumothorax: >7 days	2.2	0
Emphysema	0	0

Shah PL, et al. Thorax 2013;0:1–7. doi:10.1136/thoraxjnl-2013-203743

CRVP: NETT study

- Postoperative mortality: 5.5%
- Morbidity: 58.7%:
  - Major pulmonary morbidity 30%
  - Cardiac morbidity 20%

Effectiveness Results (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

Sciurba FC. NEJM 2010; 363: 1233-1244.

Effectiveness Results (6 months)

Outcome	Endobronchial-Valve Therapy (N=220)	Control (N=101)	Between-Group Difference in Change from Baseline	P Value
	number (95% confidence interval)			
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

Sciurba FC. NEJM 2010; 363: 1233-1244.

Conclusions

CONCLUSIONS

Endobronchial-valve treatment for advanced heterogeneous emphysema induced modest improvements in lung function, exercise tolerance, and symptoms at the cost of more frequent exacerbations of COPD, pneumonia, and hemoptysis after implantation. (Funded by Pulmonx; ClinicalTrials.gov number, NCT00129584.)

Sciurba FC. NEJM 2010; 363: 1233-1244.

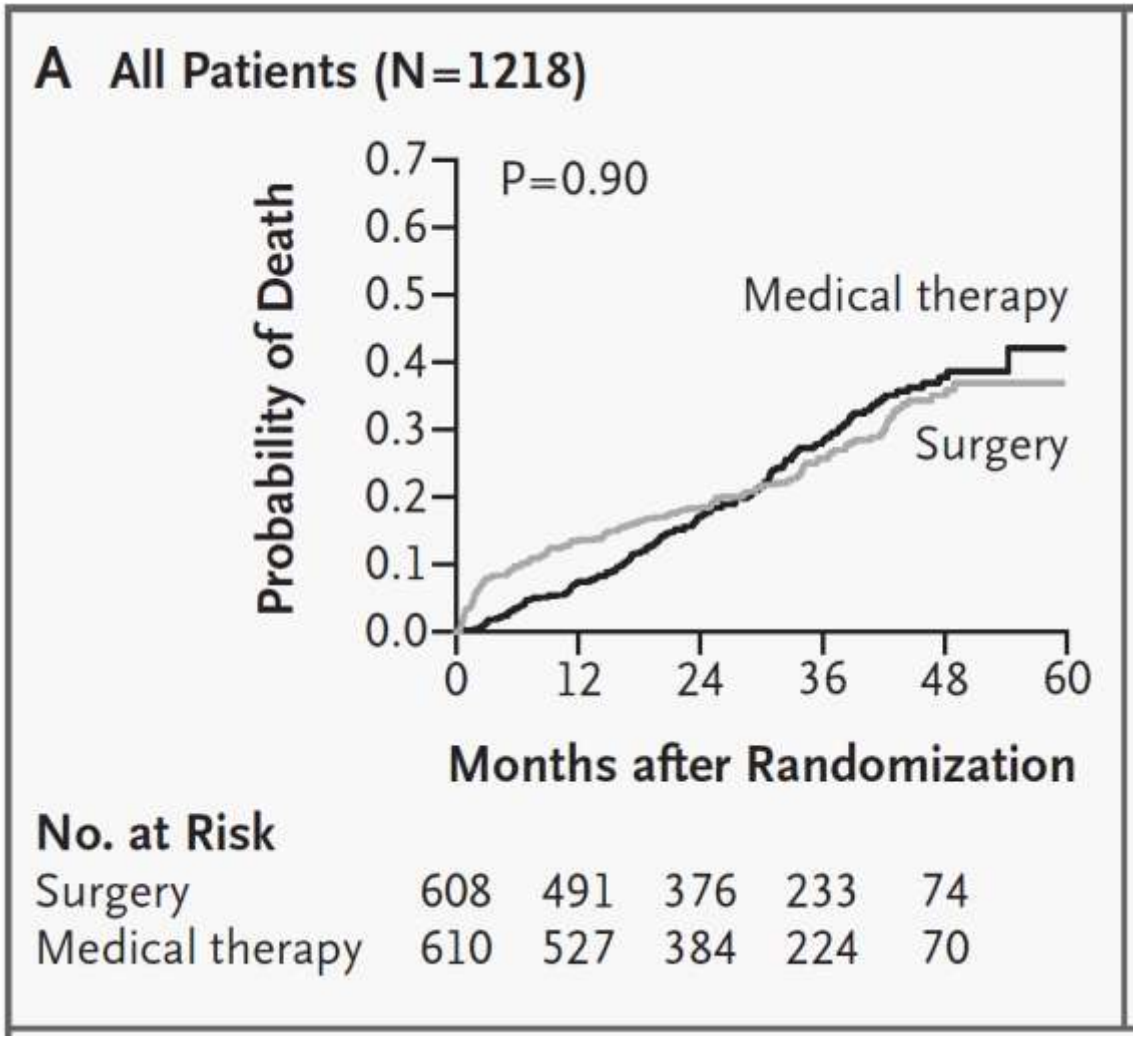
BET procedures

The extensively tested BET approaches with valves are safer but far less effective than LVRS…

Berger RL. CHEST 2010; 138:407–417

Results of NETT

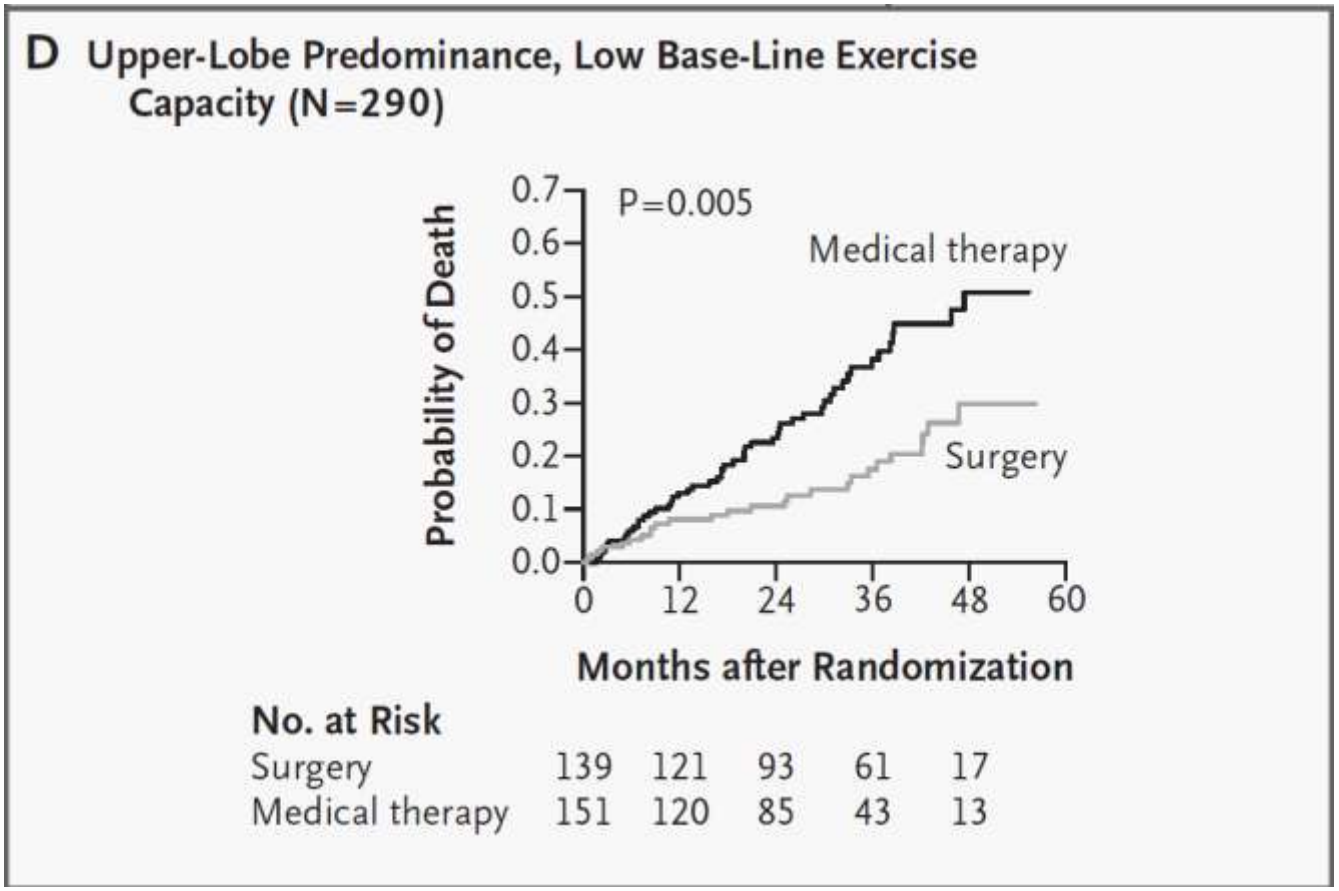
25.8% vs 26.2%



N Engl J Med 2003;348:2059

Emphysema & Lung Volume Reduction: Results of NETT

(18.7% vs 33.8%)

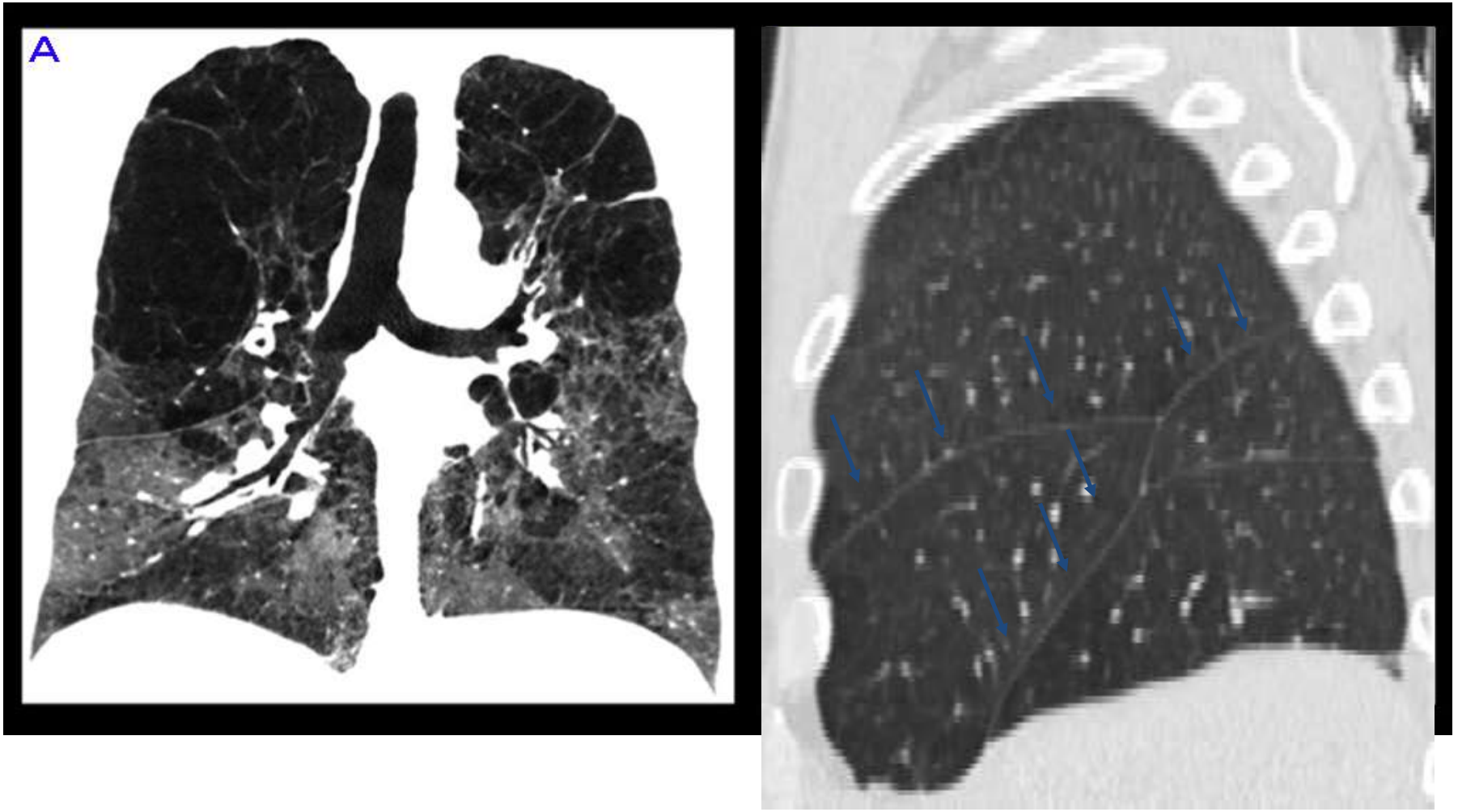


N Engl J Med 2003;348:2059

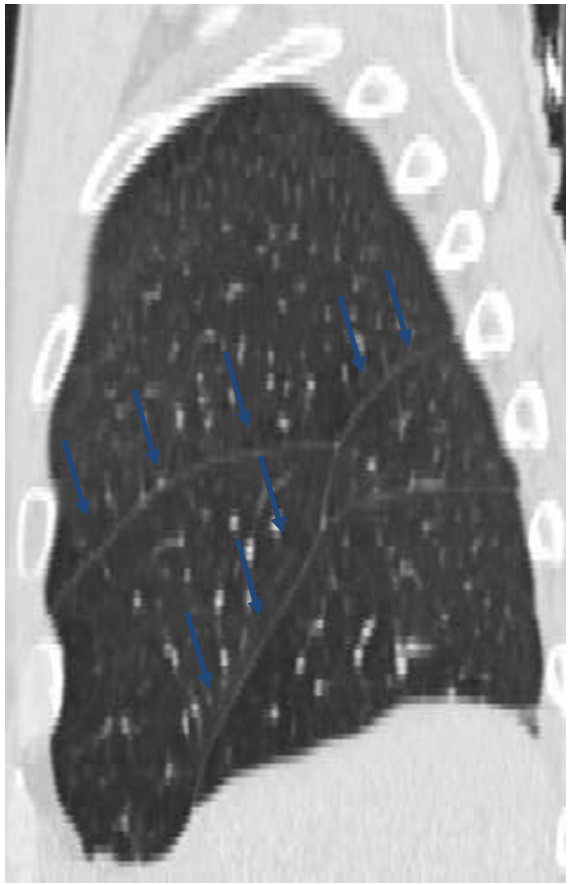
Anàlisis derivades de les dades (post-hoc analysis):

Són anàlisis estadístiques que no s'especifiquen en el protocol de l'assaig, i normalment els suggereixen les dades.

Post-hoc analysis: Heterogenicity/Complete fissures



Post-hoc analysis:Complete fissures



- Thin-slice HRCT categorical assessment of lobar fissures surrogate for inter-lobar communication
- Complete fissure(s) highly correlated with % volume reduction (CT) and % change in FEV_1

Sciurba FC. NEJM 2010; 363: 1233-1244.

Post-hoc analysis: Heterogenicity/Complete fissures

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

Sciurba FC. NEJM 2010; 363: 1233-1244.

Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort

Felix J.F. Herth, Marc Noppen, Arschang Valipour, Sylvie Leroy, Jean-Michel Vergnon, Joachim H. Ficker, Jim J. Egan, Stefano Gasparini, Carlos Agusti, Debby Holmes-Higgin and Armin Ernst, on behalf of the International VENT Study Group

- Multi-center
- Prospective/Randomized
  - 2:1 treatment to control / non-blinded (111 patients/60controls)
- same entry criteria
- same methodology

Hertz FJ, ERJ 2012:39: 1334-1342.

Efficacy predictors: European Cohort

	Complete fissure			Incomplete fissure		
	EBV	Control[#]	p-value	EBV	Control	p-value
Patients n	44	19		67	40	
Δ FEV_1 %						
6 months	16±21	2±14	0.02	1±18	-1±21	0.7

Hertz FJ, ERJ 2012:39: 1334-1342.

Clinical effectiveness: Complete fissures and lobar occlusion

	Complete fissure		
	Lobar occlusion	No lobar occlusion	p-value#
Δ FEV1 %			
6 months	26±24	6±12	0.004
12 months	28±32	2±10	0.005
⩾15% improved	12 (67)	1 (8)	0.002
Δ cycle ergometry workload W			
6 months	8±15	0±14	0.10
12 months	6±16	5±10	0.9
⩾10 W improved	8 (44)	3 (27)	0.4
Δ 6MWD %			
6 months	22±38	-2±19	0.03
12 months	22±40	0±20	0.06
⩾35 m improved	10 (56)	3 (25)	0.1

Hertz FJ, ERJ 2012:39: 1334-1342

RCT: endobronchial valves

Table 2 Changes in outcome measurements from baseline according to fissure integrity and correct valve placement to achieve complete occlusion

	FEV_1		SGRQ		Cycle ergometry (W)	
	Valves (%)	Control (%)	Valves	Control	Valves	Control
Overall	7±20	0.5±19	−5±14	0.3±13	2±14	−3±10
Intact fissures	16±21	2±14	−6±15	3±15	4±1	−3±7
Intact fissure and correct placement	26±24	3±14	−10±15	3±15	8±15	−3±7

Shah PL, et al. Thorax 2013;0:1–7. doi:10.1136/thoraxjnl-2013-203743

Clinical effectiveness of endobronchial valves

FACTORS TÈCNICS

- Experiència broncoscopista
- Correcta elecció mida vàlvula
- Correcta colocació vàlvula

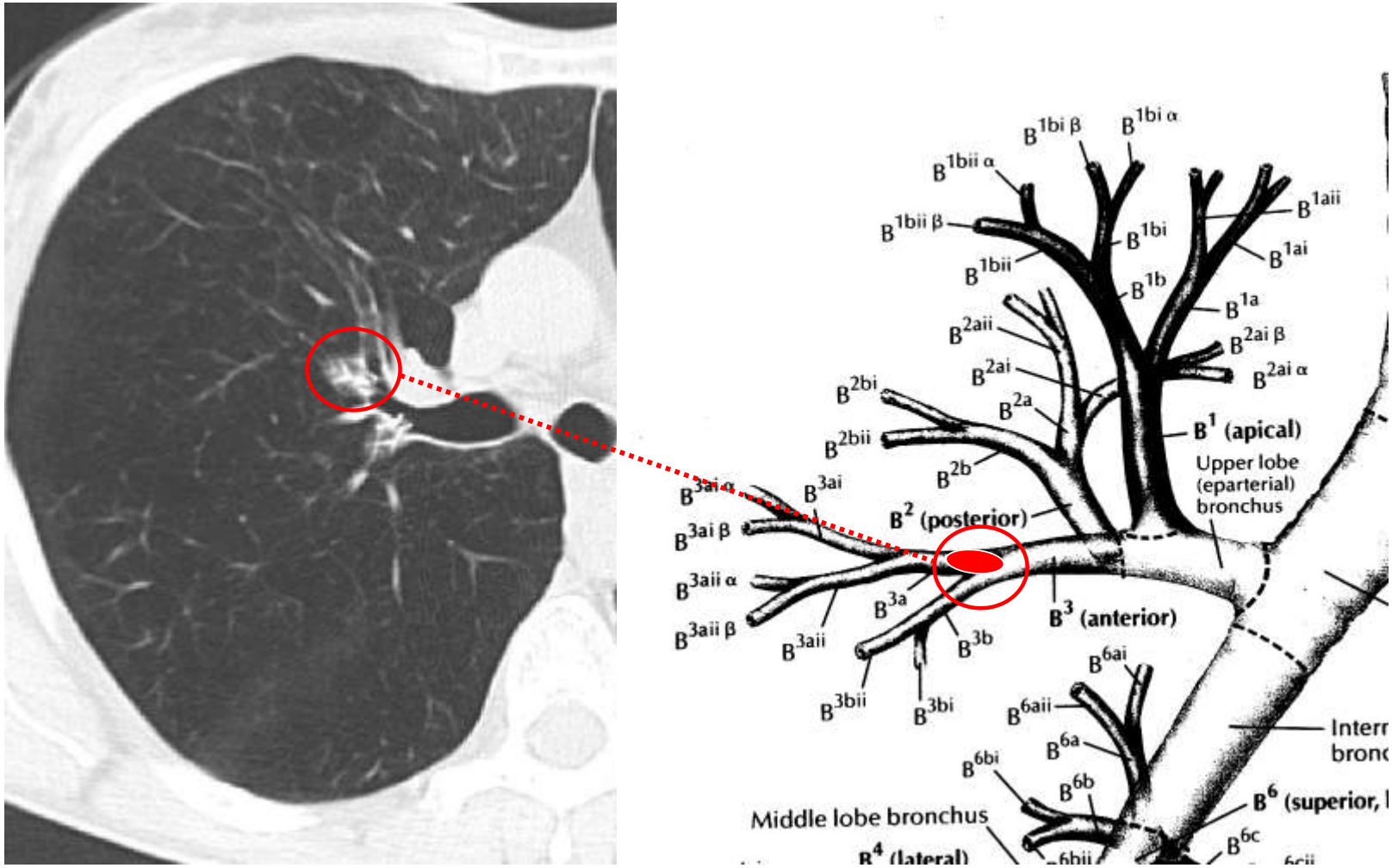
FACTORS ANATÒMICS

- Adequada “landing zone”
- Característiques del emfisema
- Presència de ventilació col.lateral

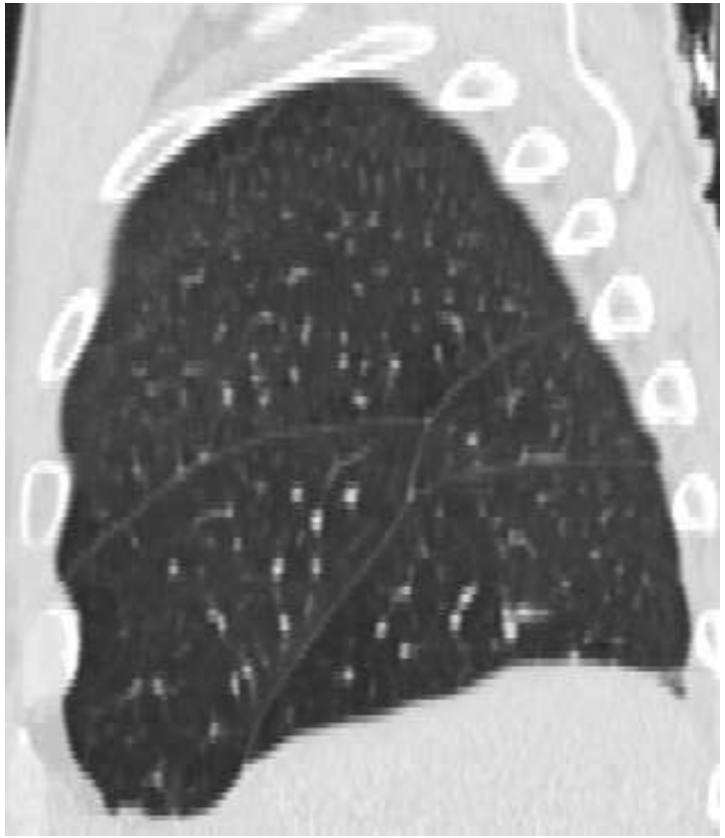
Bronchial valves

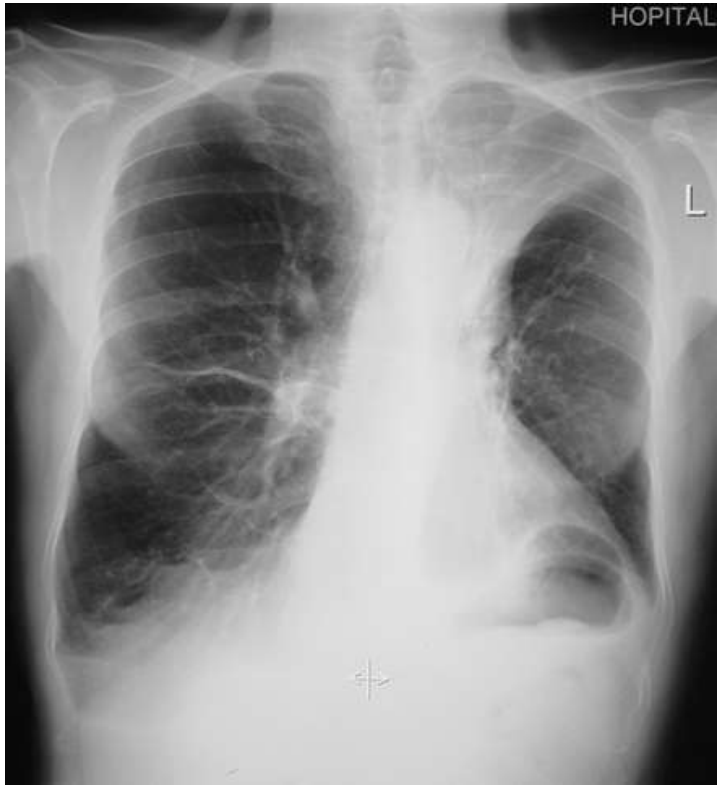
Fissure Integrity	38 %
Lobar occlusion	55 %

Lobar occlusion

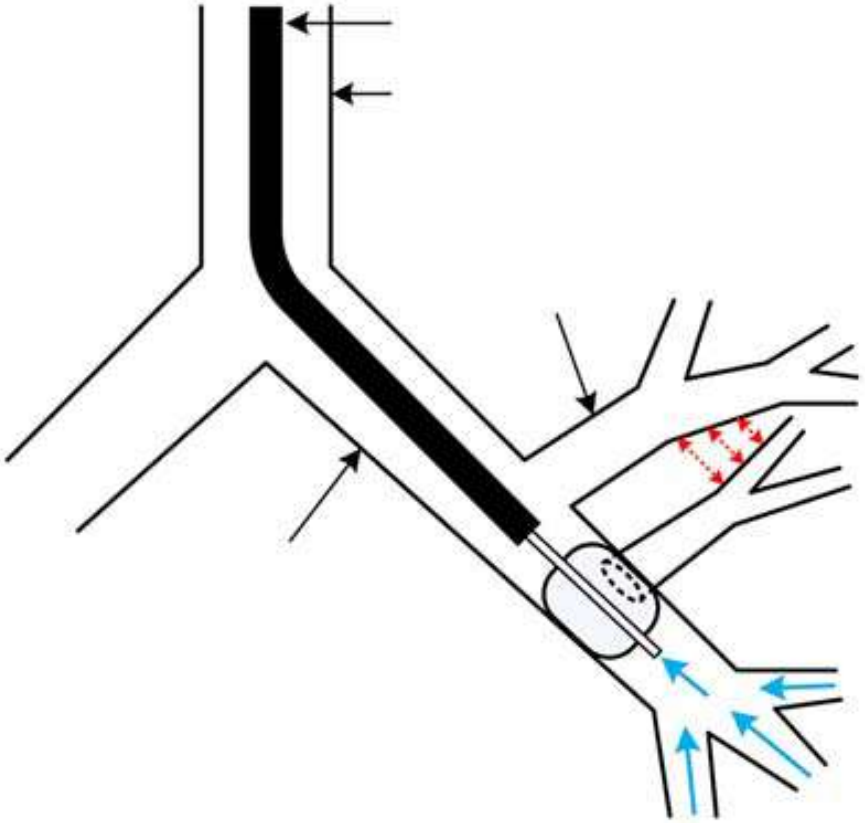


Complete fissures/Lobar oclussion



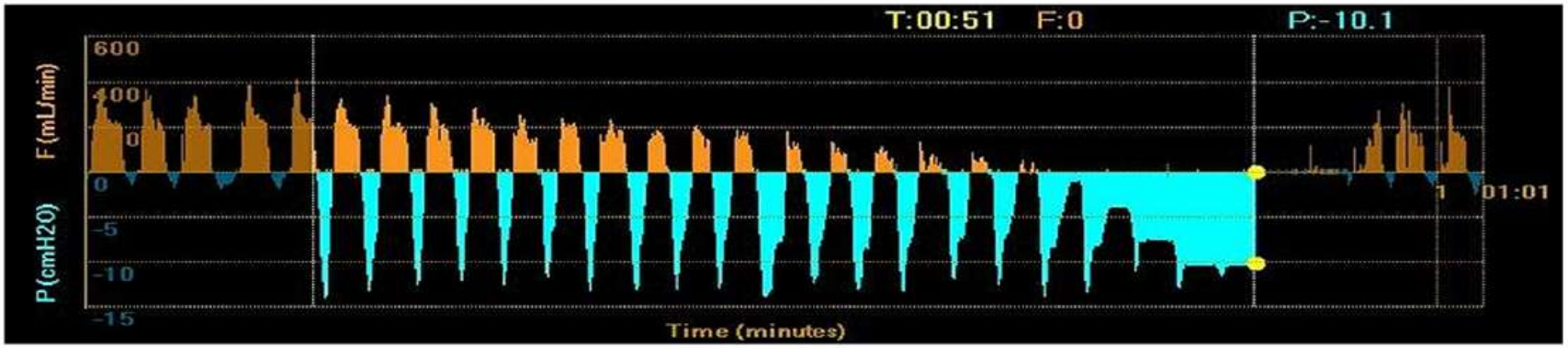


Chartis output (Pulmonx)



Chartis output (Pulmonx)

A



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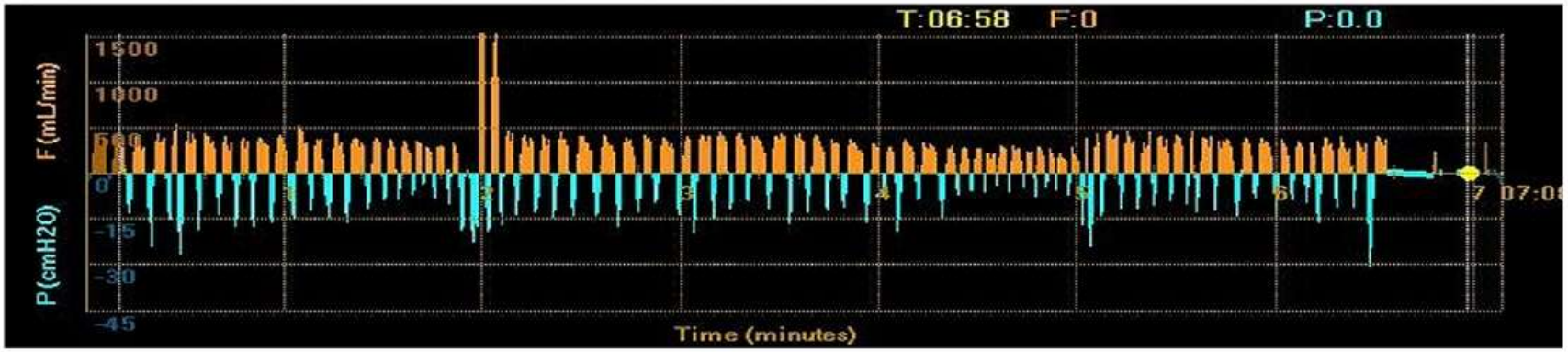
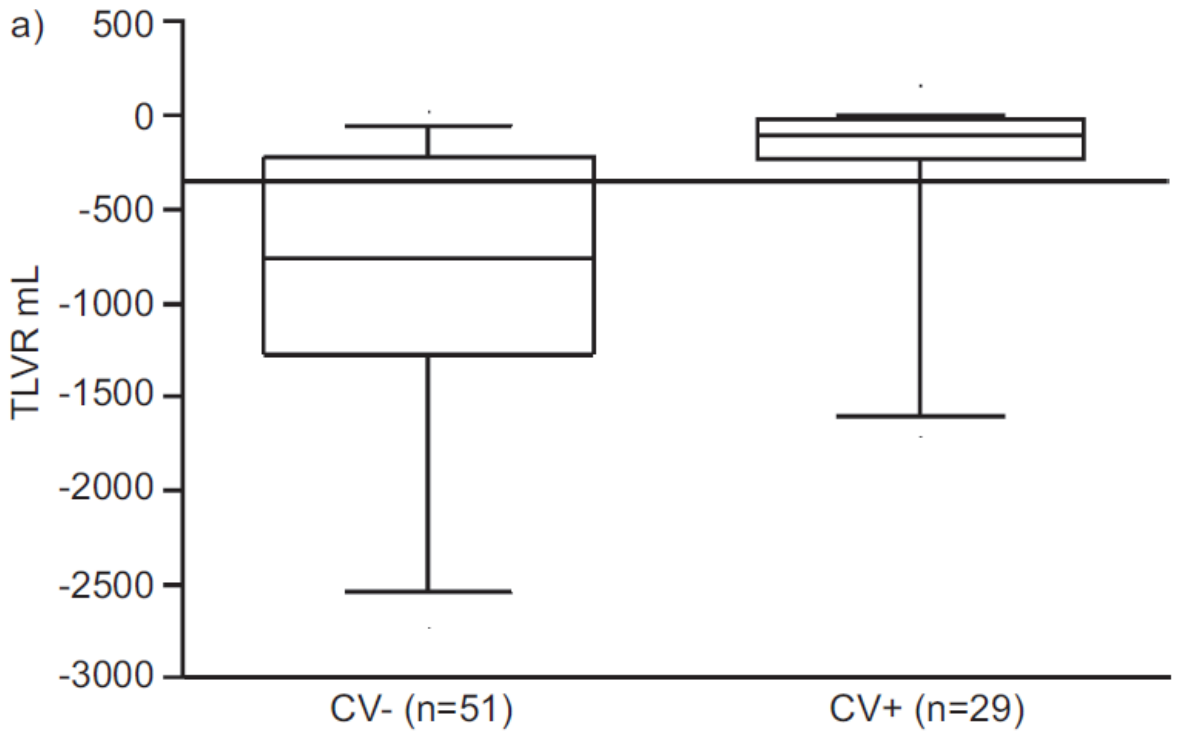


Chartis (Pulmonx)

Accuracy 75% in predicting predefined 350 ml TLVR



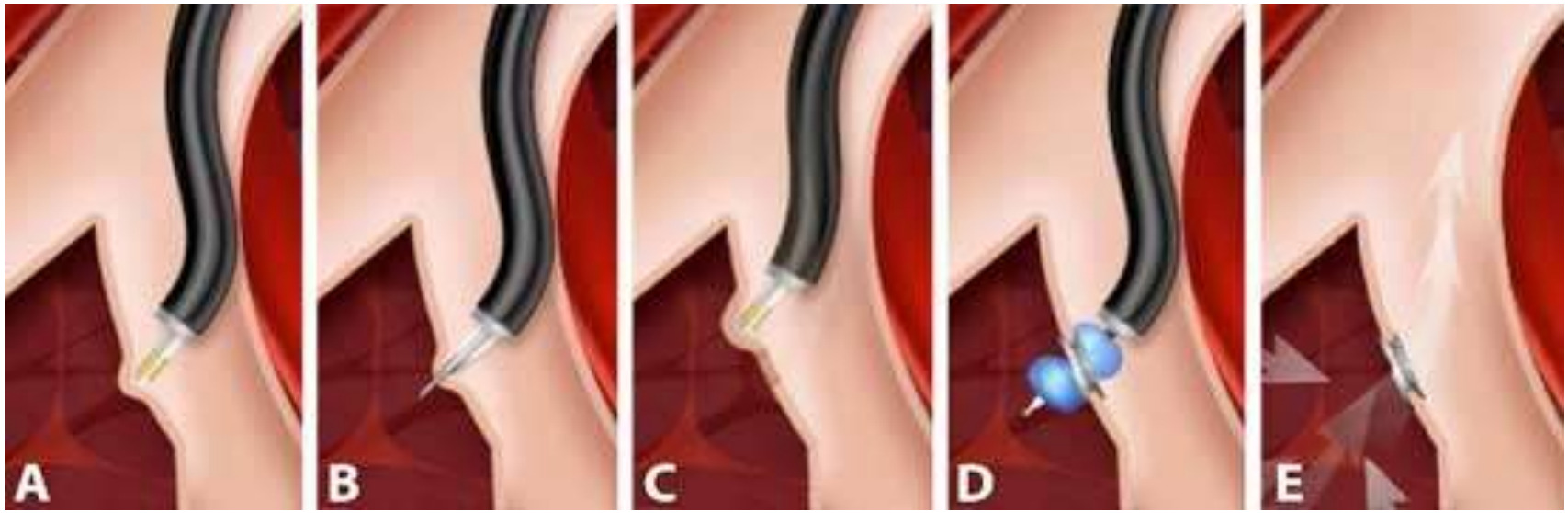
Herth FJF. ERJ 2013; 41: 302-308

What's your BET?

LVRS or BET

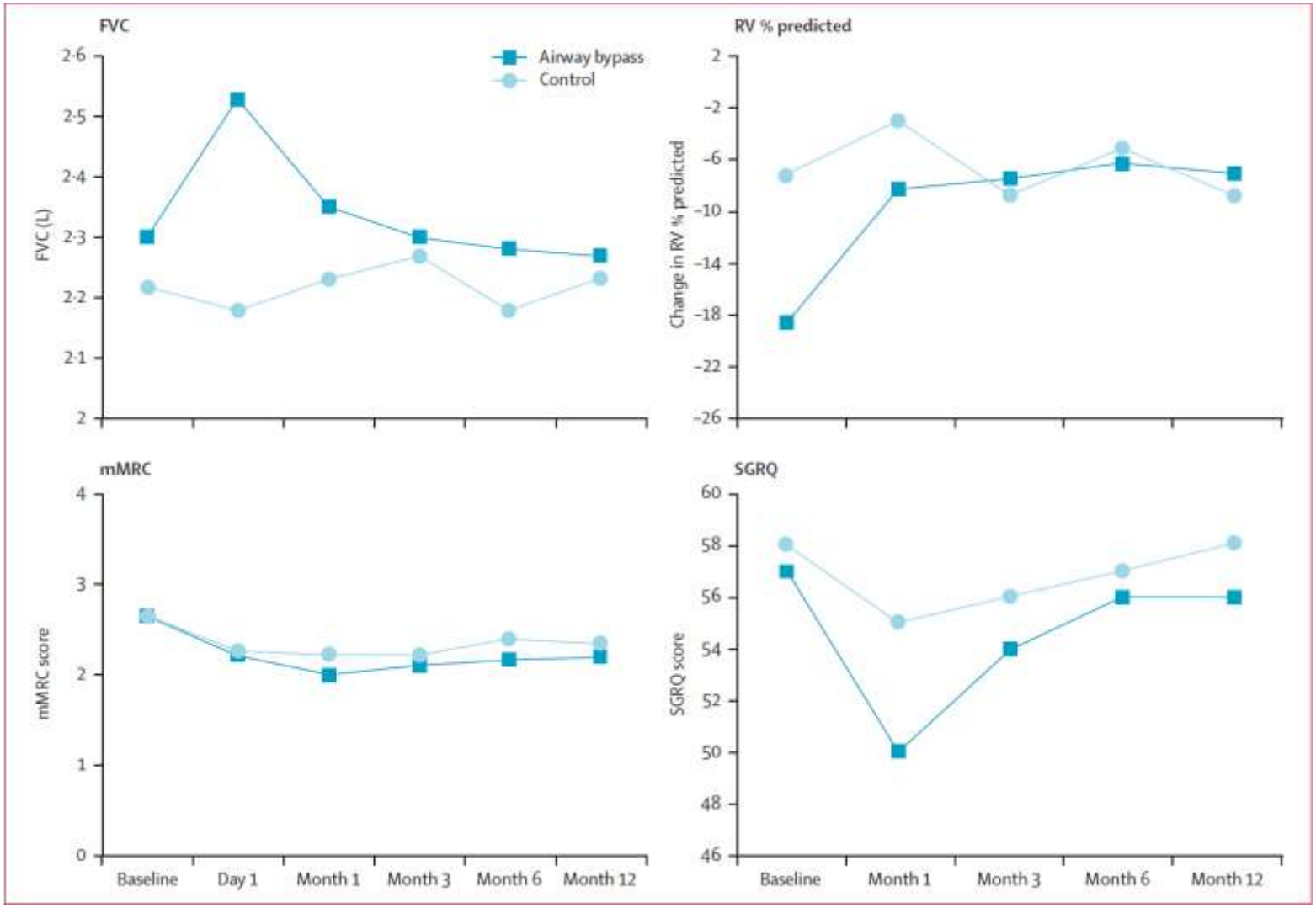
"Aixo no és el final. Ni tan sols és el inici del final. Però és, potser, el final del inici"

Airway by-pass (EasyTrial)



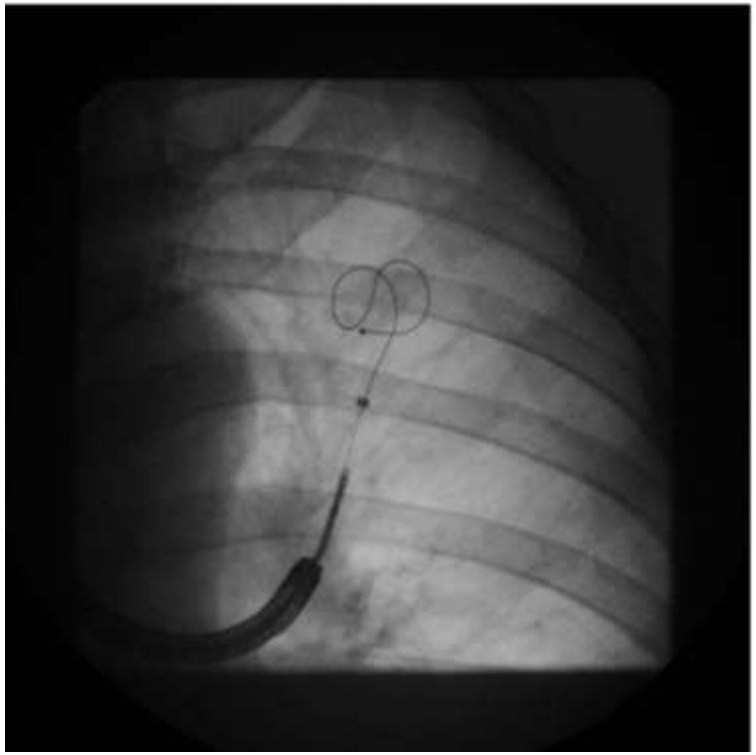
Shah PL. Lancet 2011; 378: 997-1005

Airway by-pass (EasyTrial)



Shah PL. Lancet 2011; 378: 997-1005

Endobronchial Coils (RESET)



Shah P. Lancet Respir Med 2013; 1:233-240

Endobronchial Coils (RESET)

	Treatment (n= 23)	Usual care (n= 23)	p value*
Primary outcome			
SGRQ ≥4-point improvement	15 (65%)	5 (22%)	0·01
SGRQ ≥8-point improvement	13 (57%)	3 (13%)	0·01
Secondary outcome			
Respiratory volume: 0·35-L reduction	13 (57%)	4 (17%)	0·01
6-min walk test: 26-m improvement	17 (74%)	4 (17%)	<0·0003
FEV_1: 10% improvement	13 (57%)	6 (26%)	0·07

Data are n (%). *Fisher's Exact Test. SGRQ=St George's Respiratory Questionnaire. FEV_1= forced expiratory volume in 1 s.

Table 3: Responder analysis of primary and secondary efficacy outcomes in the intent-to-treat population (change from baseline at 90 days after final treatment)

Shah P. Lancet Respir Med 2013; 1:233-240

Ongoing and future multicenter U.S.studies

Trial	Device	Primary Endpoint	Inclusion Criteria	Status
Lung Volume Reduction Coil for Treatment in Patients with Emphysema (RENEW) study	RePneu	Mean absolute 6MWD change from baseline at 12 mo	Age ⩾ 35 yr Post-bronchodilator FEV_1 < 45% predicted Subject has TLC > 100% predicted RV ⩾ 225% Subject has marked dyspnea ⩾ 2 on mMRC scale of 0–4 Smoking cessation for at least 8 wk prior Smoking abstinence for 16 wk	Recruiting patients
Study of the AeriSeal System for HyPerInflation Reduction in Emphysema (ASPIRE)	AeriSeal	Change in FEV_1 over 12 mo	Age ⩾ 40 yr Upper lobe–predominant emphysema FEV_1 < 50% predicted and FEV_1/FVC ratio < 70% TLC > 100% predicted RV > 150% predicted D_{LCO} ⩾ 20% and ⩽ 60% predicted Blood gases and oxygen saturation showing both: Sp_{O_2} ⩾ 90% on ⩽ 4 L/min supplemental O_2 and Pa_{CO_2} < 65 torr	Terminated
Evaluation of the IBV Valve for Emphysema to Improve Lung Function (EMPROVE)	IBV	Change in FEV_1 over 6 mo	6MWD ⩾ 140 m Cessation from cigarette smoking for 4 mo Pulmonary function testing: FEV_1 ⩽ 45% predicted, RV ⩾ 150% predicted, TLC ⩾ 100% predicted	Recruiting patients
Lung Function Improvement after Bronchoscopic Lung Volume Reduction with PulmonX Endobronchial Valves used in Treatment of Emphysema (LIBERATE STUDY)	Zephyr Charitis	Change in FEV_1 over 12 mo	Clinical and radiological evidence of emphysema Currently nonsmoking Stable on current medication FEV_1 between 15% and 45% predicted	Not yet recruiting

Lee HJ. Ann Am Thorac Soc 2013; 10: 667-679

What's your bet ?

- No direct comparison between BETs and LVRS.
- No clear primary end points.
- No radiologic guidelines to select patients.
- LVRS limited to upper lobe heterogeneous emphysema.
- BET not limited to these criteria but determinated by the presence or absence of Colateral Ventilation.

En quins pacients posaria vàlvules endobronquials?

Sovint li dic als meus pacients: "Si pogués extirpar els teus lòbuls superiors, sé que milloraries molt, amb menys ofec i amb una millor respiració... Desgraciadament, no puc sotmetre't a una intervenció quirúrgica. Tens problemes cardíacs i vasculars. En el teu cas, el risc és molt alt".

Aquest és el pacient que, al meu entendre, hauria de ser considerat per al tractament amb vàlvules endobronquials"

Joel D. Cooper , MD, FCCP

J Thorac Cardiovasc Surg 2010; 140: 564-572

Endobronchial valves:
Other Uses

- Malaltia bullosa.
- Fístules tràqueo bronquials.
- Pont per al trasplantament.
- Hiperinsuflació pulmonar post-trasplantament.