Thomas Malfait – Dienst Longziekten UZ Gent
Frédéric Deryck – Dienst TVHK UZ Gent

Wat als de medicamenteuze therapie voor COPD faalt?

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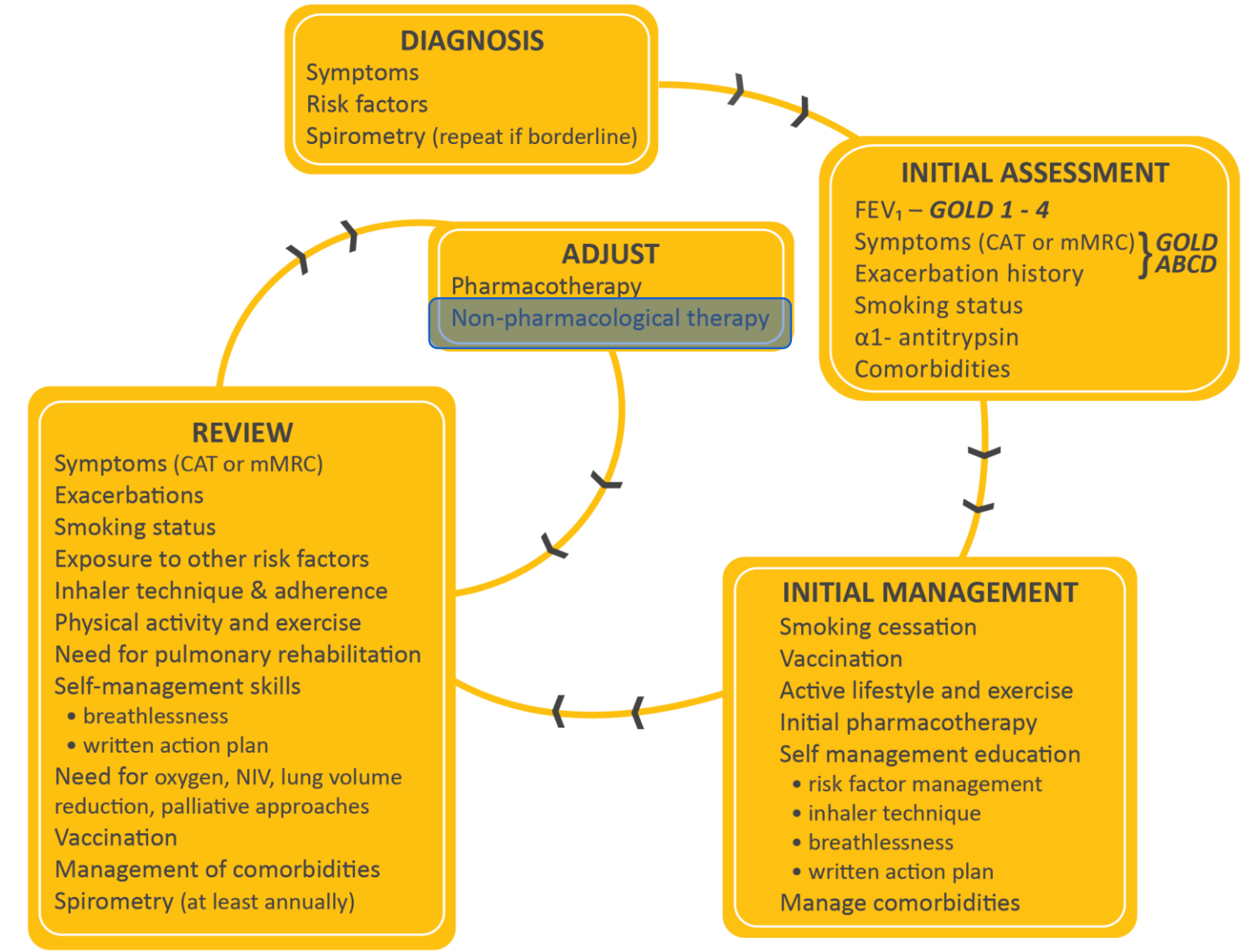
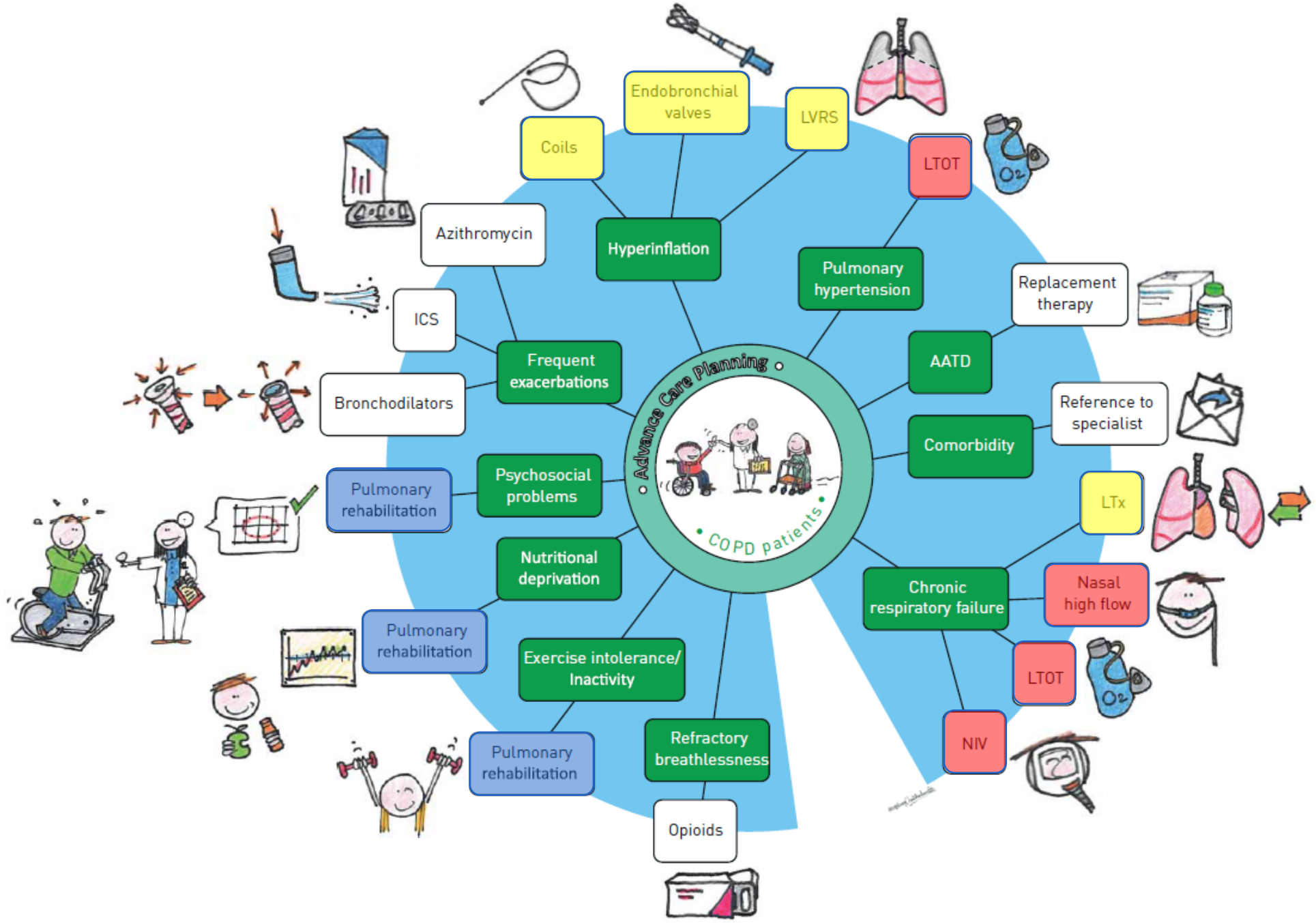
UNIVERSITEIT GENT

MANAGEMENT OF COPD





MARLIES VAN DIJK ET AL. - TREATMENT OF SEVERE STABLE COPD: THE MULTIDIMENSIONAL APPROACH OF TREATABLE TRAITS - ERJ OPEN RESEARCH 2020 6: 00322-2019; **DOI:** 10.1183/23120541.00322-2019

Thomas Malfait – Dienst Longziekten UZ Gent

Wat als de medicamenteuze therapie voor COPD faalt?

- Long Volume Reductie (LVR)
- Longtransplantatie (LTx)

UZ GENT

UNIVERSITEIT GENT

Background

- COPD causes significant morbidity and mortality.

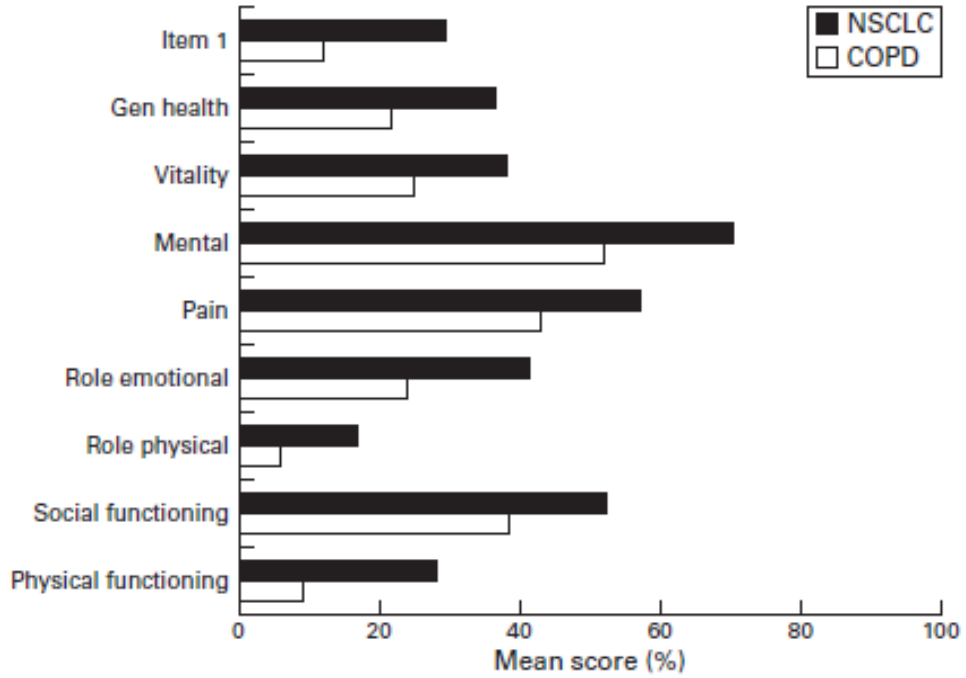


Figure 1 Mean SF-36 scores (scale 0–100%). All dimensions except roles physical and emotional = p≤0.05 (Mann-Whitney U test). Gen health = general health; item 1 refers to how patients rate their general health. A higher score indicates a more favourable health status.

Table 2 Depression subscale of Health Anxiety and Depression Scale (HADS) for the two groups

	Mean (SD)	*Range*
COPD	10.18 (3.95)	3–21
NSCLC	7.22 (5.16) p<0.01	0–20

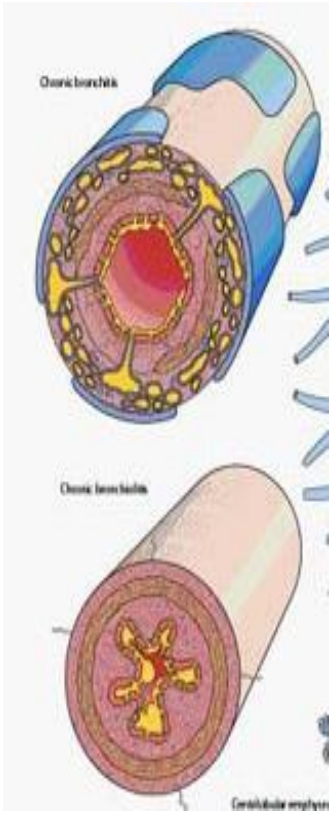
Scale 0–21: ⩾8–10 indicative of clinical depression.[15]

Table 3 Anxiety subscale of the Hospital Anxiety and Depression Scale for the two groups

	Mean (SD)	*Range*
COPD	11.44 (4.76)	1–20
NSCLC	7.20 (5.25) p<0.0001	0–21

Scale 0–21: ⩾8–10 indicative of clinical anxiety.[15]

Gore JM, Brophy CJ, Greentstone MA. How well do we care for patients with end stage chronic obstructive pulmonary disease (COPD?). A comparison of palliative care and quality of life in COPD and lung cancer. *Thorax* 2000;55:1000-1006

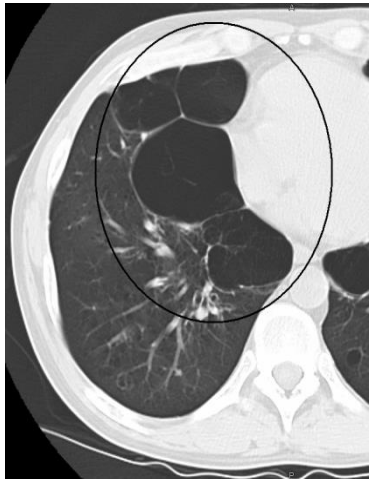


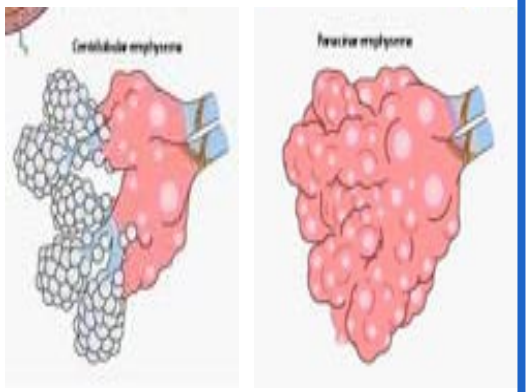
INFLAMMATION

Small airway disease
Airway inflammation
Airway remodeling

Parenchymal destruction
Loss of alveolar attachments
Decrease of elastic recall

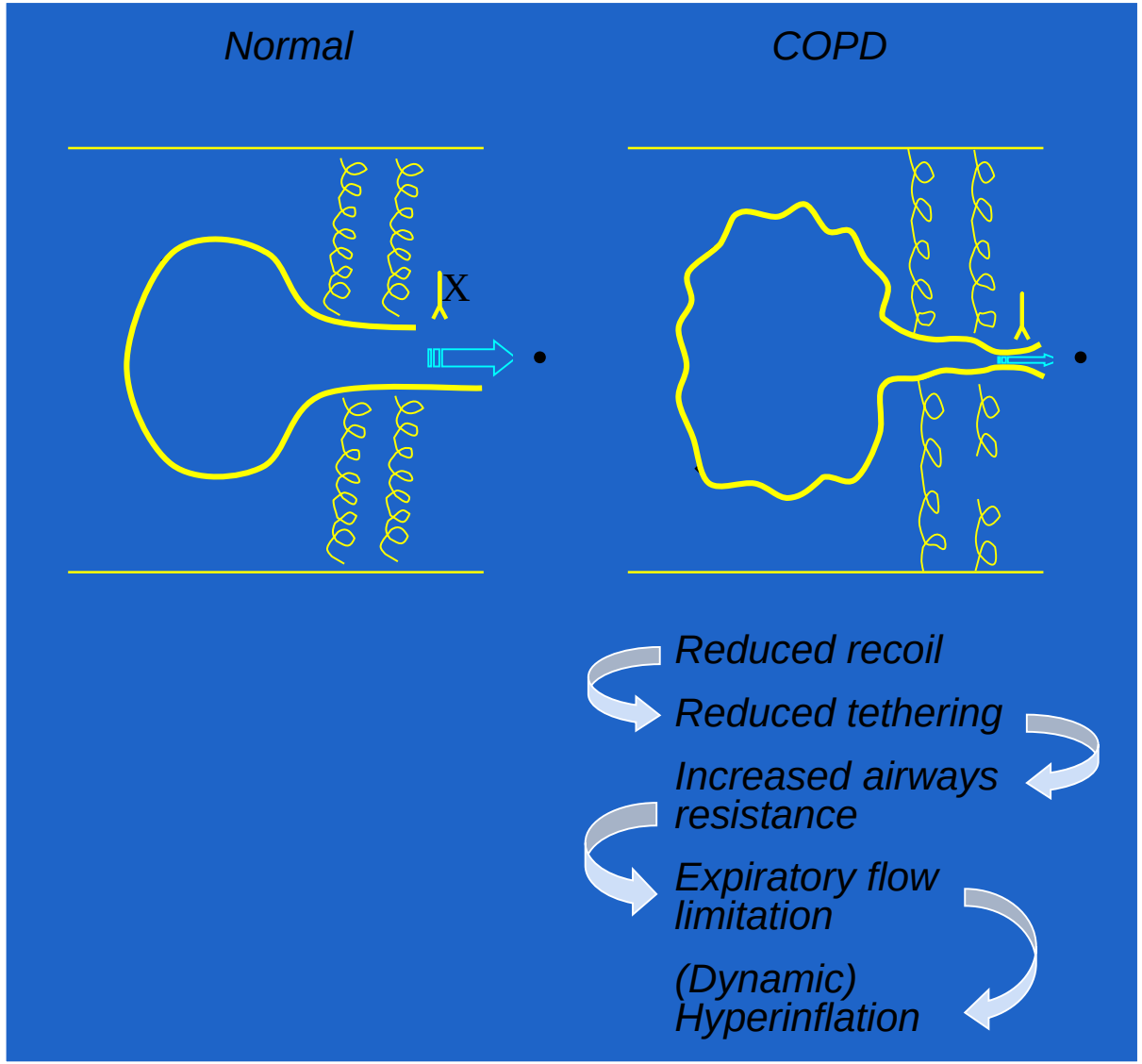
AIRFLOW LIMITATION



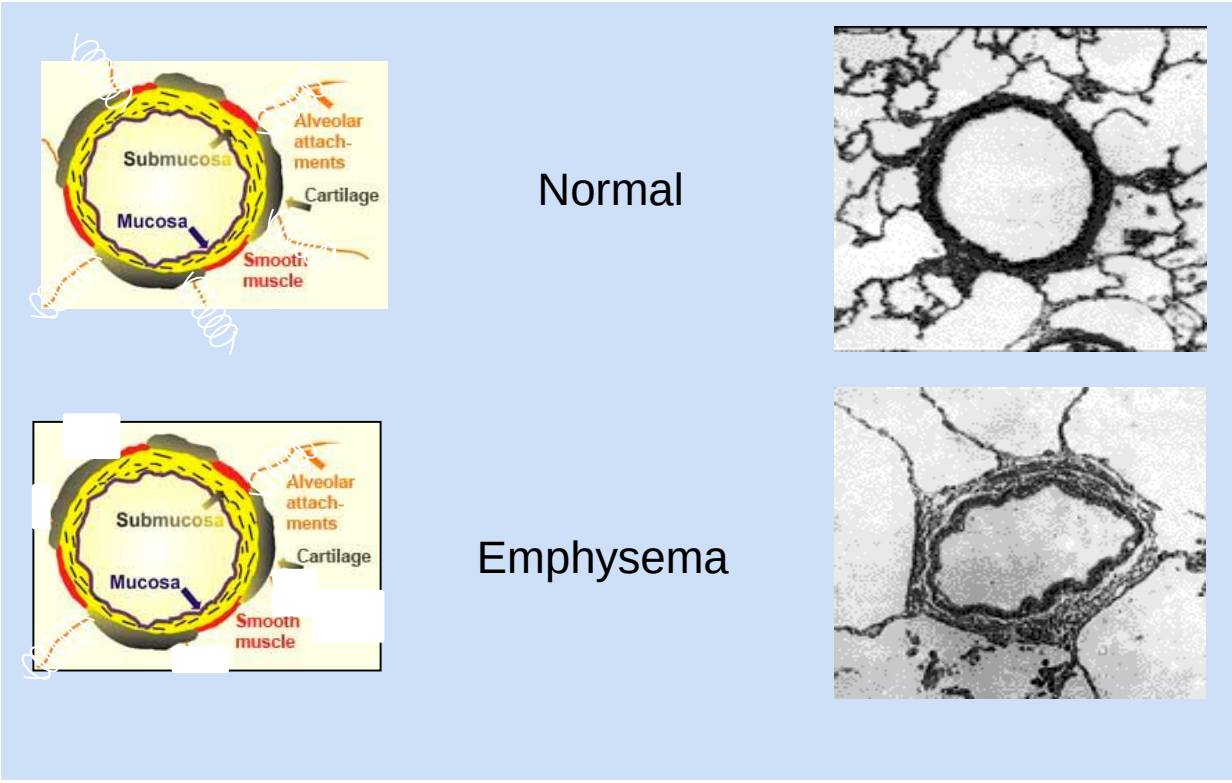


Cough + Sputum

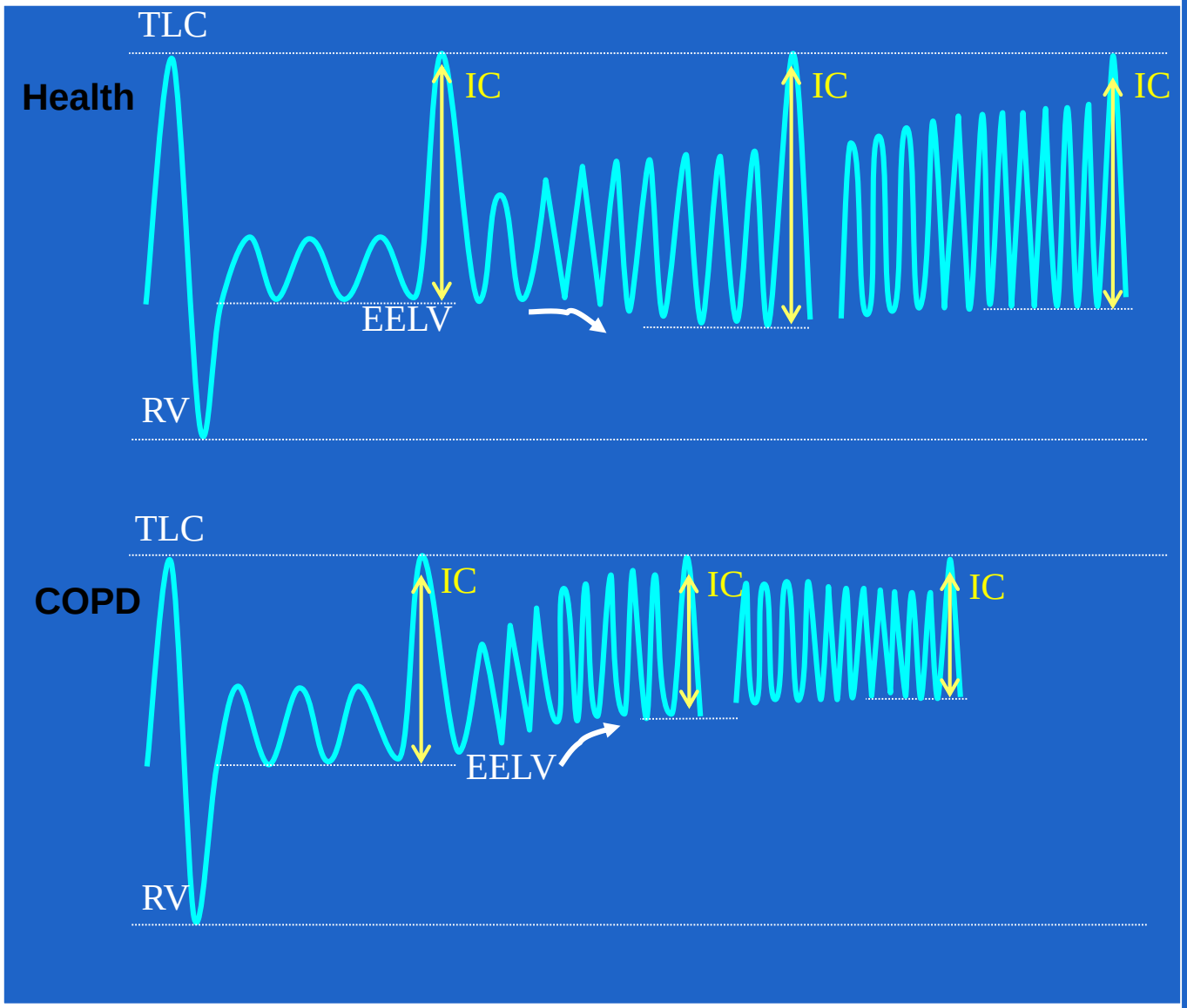
Dyspnea d'effort

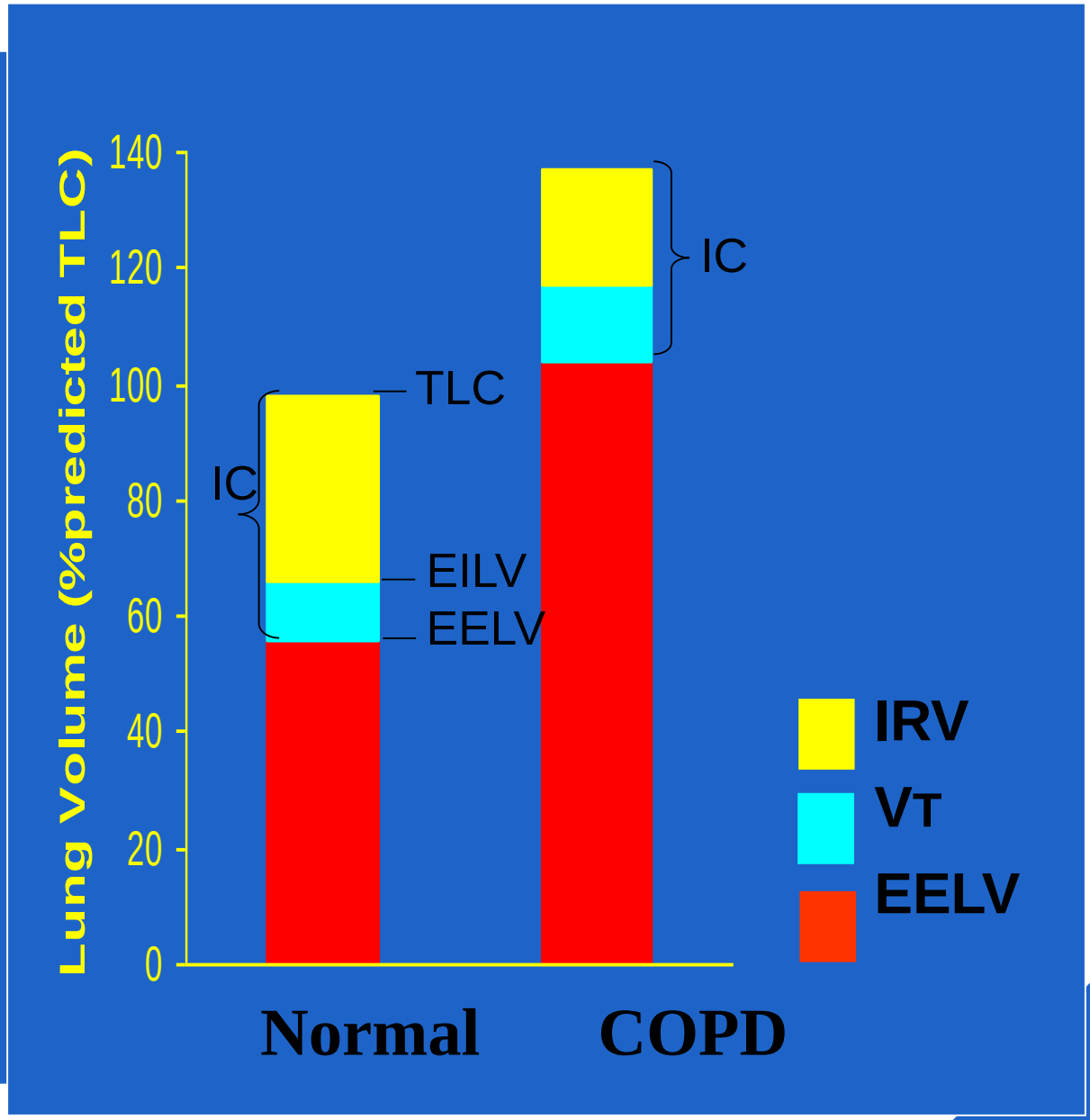


Courtesy of O'Donnell DE



LVRC's: Mechanisms of action & overview of clinical results – P Shah – ERS 2013

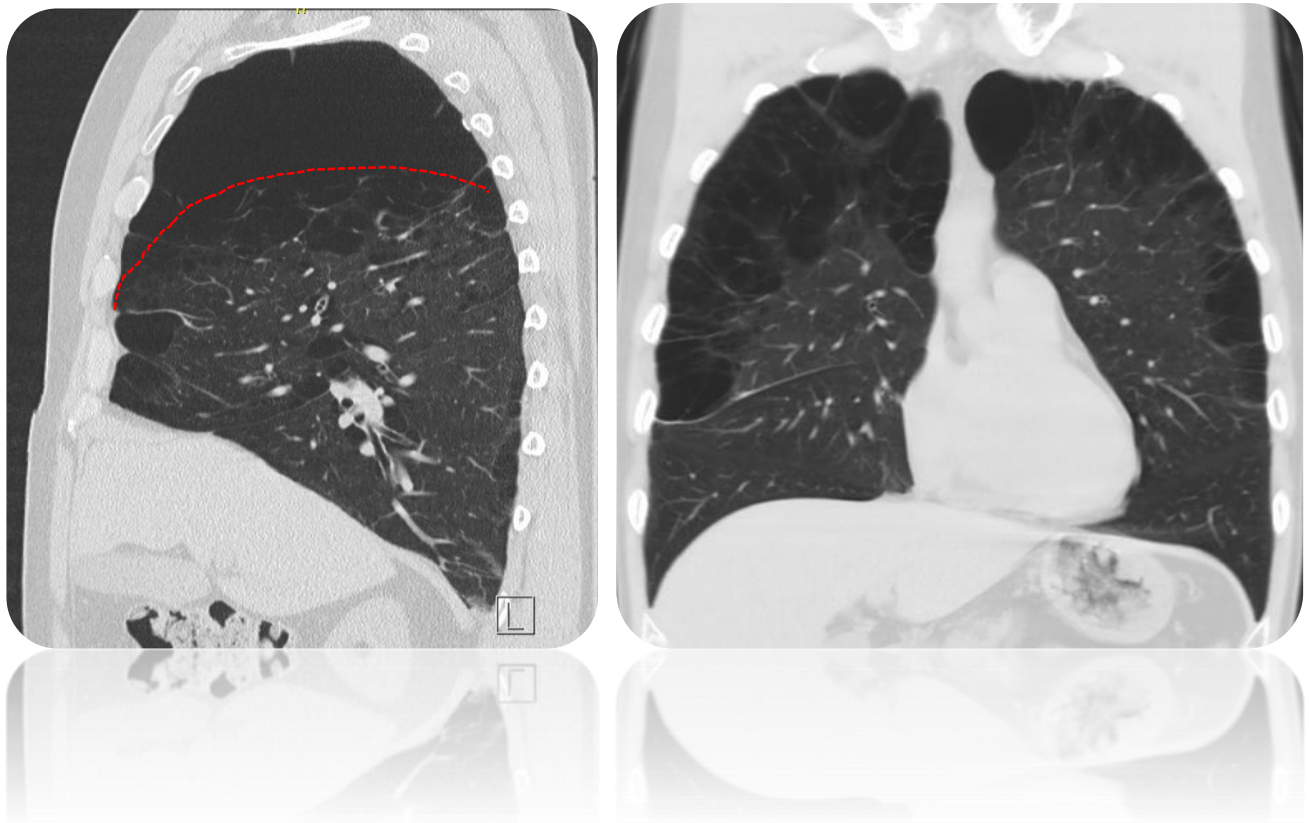




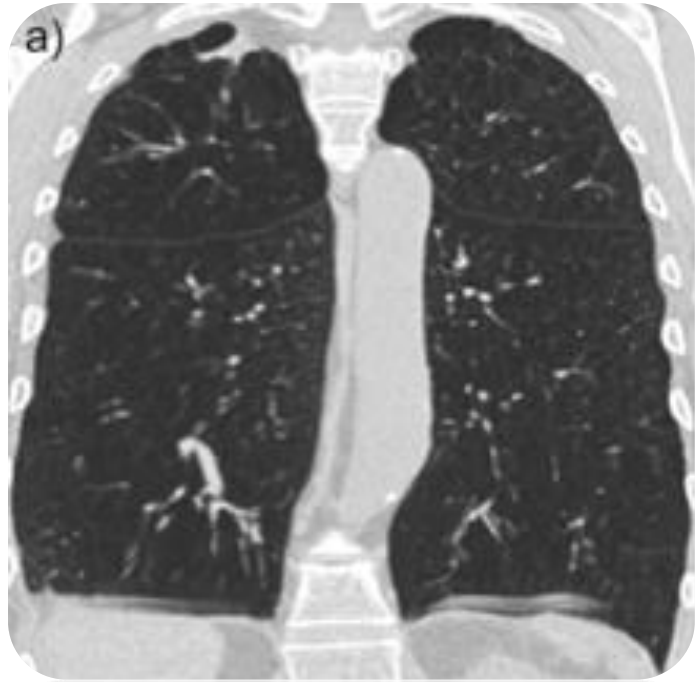
Courtesy of O'Donnell DE

!! Not all emphysema is alike !!

Heterogeneous



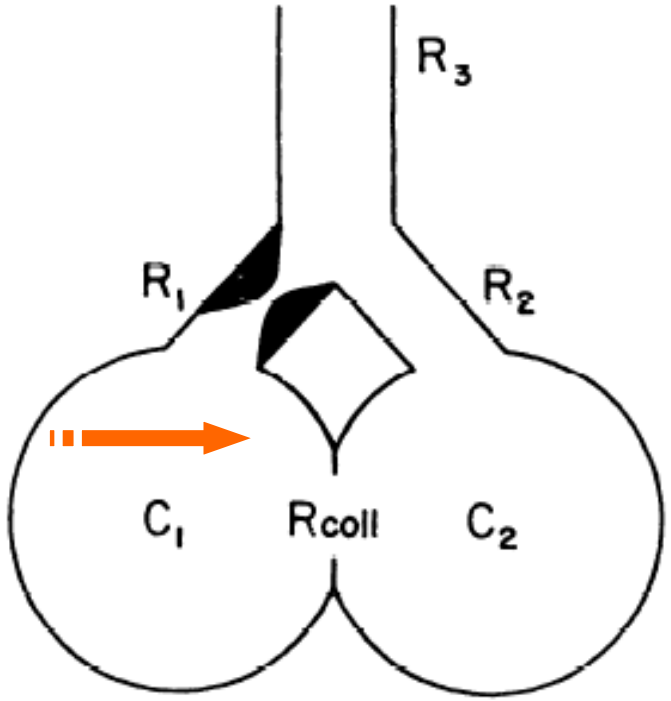
Homogeneous



!! Not all emphysema is alike !!

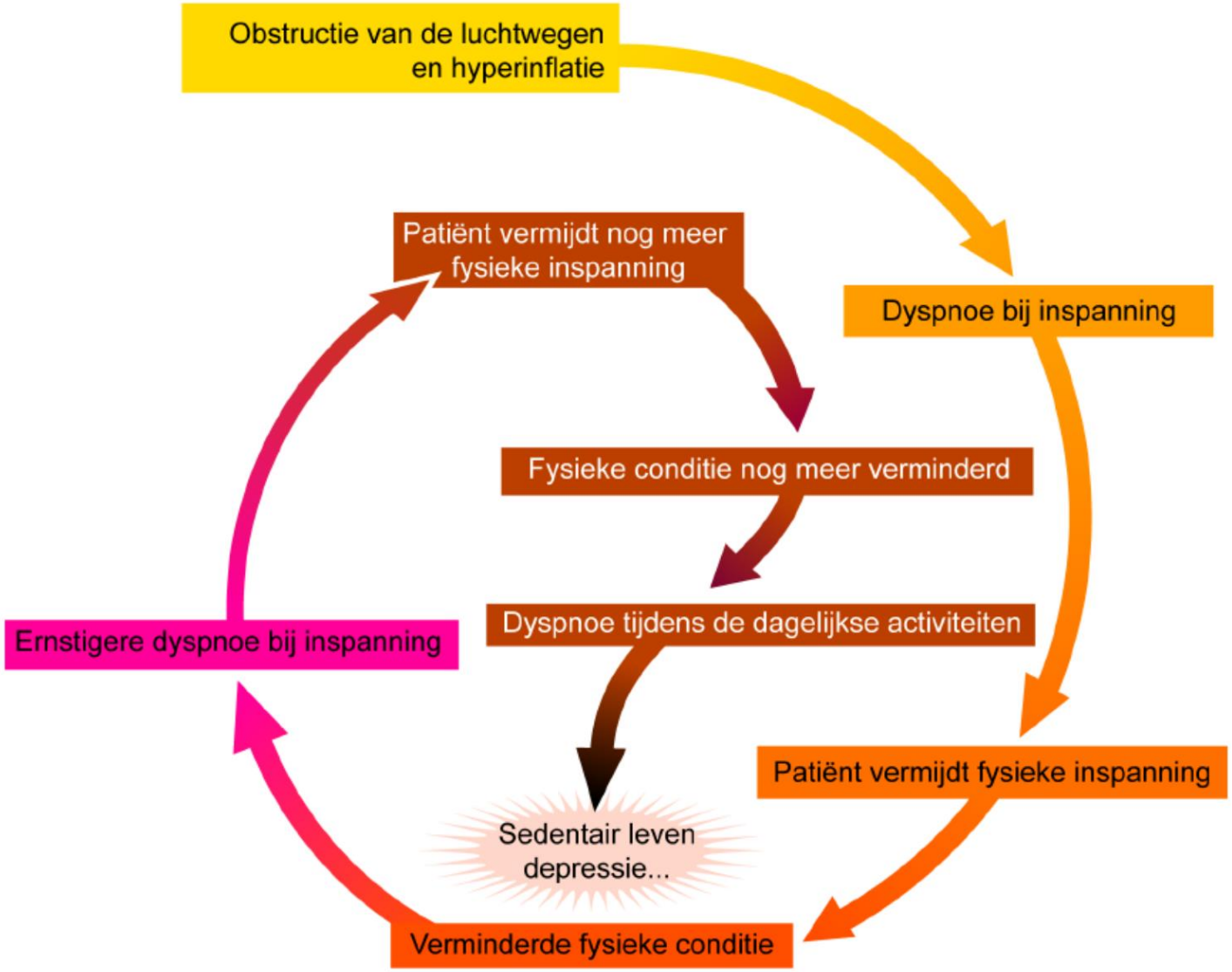
Collateral Ventilation

- Collateral channels with high resistance
  1. Interalveolar
  2. Bronchiole-alveolar
  3. Interbronchiole
  4. Interlobar



- In normal individuals : No flow
- When peripheral airways become obstructed or obliterated in emphysema, collateral channels may provide for more even distribution of ventilation

De patient met ernstig longemfyseem



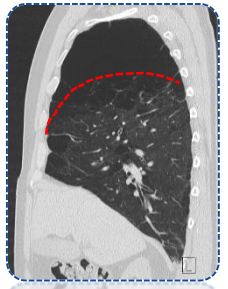
of breathing

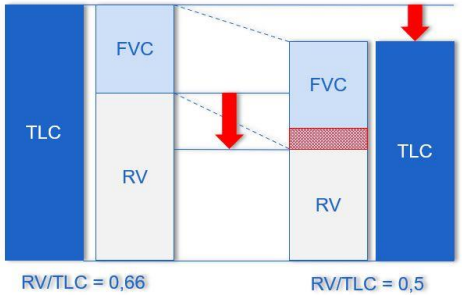
cles at a mechanical disadvantage

r pressure to overcome to initiate breath

ional) Breathlessness

Rationale Long Volume Reductie (LVR)





Verminderen overtollig residueel volume
remodellering/verkleinen van de long

↘ mismatch longvolume/volume thoraxholte

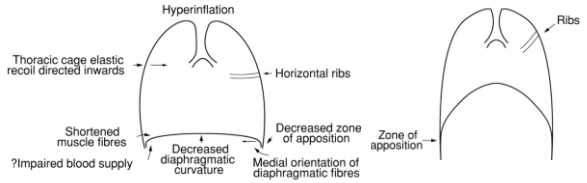
↗ elastische recoil

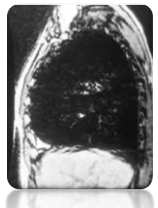
↗expiratie airflow

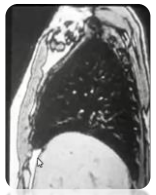
↘ hyperinflatie

↘FRC ↘RV ↘ TLC

↗functie diafragma & intercostaalspieren
↘ ademhalingsarbeid







reëxpansie gezonder parenchym

↗endotheliale functie & gasuitwisseling

↘intrathoracale druk

↗cardiale functie

- verminderen hyperinflatie
- verbeteren van respiratoire mechaniek

Het prille begin van LVRS

1959

Otto C. Brantigan, MD
(1904-1981)

A SURGICAL APPROACH TO PULMONARY EMPHYSEMA[1]

OTTO C. BRANTIGAN, EUGENE MUELLER, AND MILTON B. KRESS

Introduction

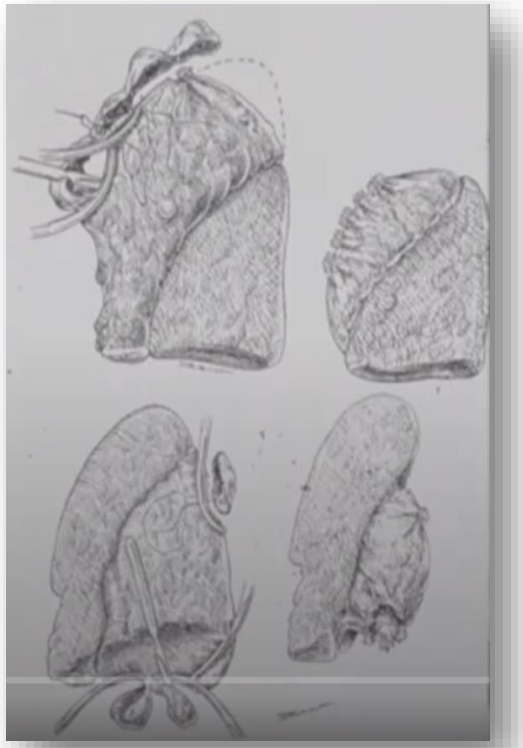
After eight years of study by trial and error methods, an operation has evolved designed to restore a well-known physiologic mechanism that has, for the most part, been lost in the patient with idiopathic, hypertrophic, obstructive pulmonary emphysema. It is an operation directed at restoration of a physiologic principle. It is not concerned with the removal of pathologic tissue.

Analysis of Problem

Definition of emphysema: Emphysema is characterized by physiologic airway obstruction which affects expiration more than inspiration; pathologically organic obstruction cannot be demonstrated. Physiologic measurements reveal obstruction to the airway and reduced ventilation. By ausculatory methods the breath sounds are found to range from diminished to absent sounds over the entire chest. The breath sounds further diminish or disappear after cough. The thorax may be barrel-shaped. Roentgenographically the lung markings appear reduced from normal (figure 108). The anteroposterior diameter of the chest is increased. The diaphragms are flattened and often steplike at their attachment to the costal margin.

can be accepted as correct and true, it is easy to show how the disturbed physiologic mechanism can be altered by operation.

In idiopathic, hypertrophic, obstructive pulmonary emphysema the disease is generalized in the lungs. There are no areas of normal lung tissue; however, all areas of the lung are not involved equally by the pathologic process (figure 109). The areas of the lung most involved pathologically are usually located about the periphery of the lobe. The areas of lung tissue with the most extensive pathologic changes are functionless as respiratory tissue. The emphysematous lung has lost its elasticity to a greater or less degree, and this is true whether or not definite changes can be demonstrated in the elastic tissue. Vascular changes with degeneration of the capillary beds are noted when lung tissue is destroyed to the greatest degree by the pathologic process, and this causes a greater or lesser degree of pulmonary hypertension. The lung volume is greater than normal (1–3) (figure 109). The thorax in the emphysematous patient is more or less fixed in a state of full inspiration, and the diaphragms are lowered or depressed.



Zeer hoge mortaliteit (16-20%)

Reïntroductie van LVRS

1995

Joel D. Cooper, MD

Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease

We undertook surgical bilateral lung volume reduction in 20 patients with severe chronic obstructive pulmonary disease to relieve thoracic distention and improve respiratory mechanics. The operation, done through median sternotomy, involves excision of 20% to 30% of the volume of each lung. The most affected portions are excised with the use of a linear stapling device fitted with strips of bovine pericardium attached to both the anvil and the cartridge to buttress the staple lines and eliminate air leakage through the staple holes. Preoperative and postoperative assessment of results has included grading of dyspnea and quality of life, exercise performance, and objective measurements of lung function by spirometry and plethysmography. There has been no early or late mortality and no requirement for immediate postoperative ventilatory assistance. Follow-up ranges from 1 to 15 months (mean 6.4 months). The mean forced expiratory volume in 1 second has improved by 82% and the reduction in total lung capacity, residual volume, and trapped gas has been highly significant. These changes have been associated with marked relief of dyspnea and improvement in exercise tolerance and quality of life. Although the follow-up period is short, these preliminary results suggest that bilateral surgical volume reduction may be of significant value for selected patients with severe chronic obstructive pulmonary disease. (J THORAC CARDIOVASC SURG 1995;109:106-19)

J. D. Cooper, MD, E. P. Trulock, MD (by invitation), A. N. Triantafillou, MD (by invitation), G. A. Patterson, MD, M. S. Pohl, RN (by invitation), P. A. Deloney, RN (by invitation), R. S. Sundaresan, MD (by invitation), and C. L. Roper, MD, *St. Louis, Mo.*

The Journal of Thoracic and Cardiovascular Surgery
Januari 1995, Volume 109, Number 1

	Before operation	*After operation*	*Percent change*	*p Value*
FEV_1 in liters (% of predicted)	0.77 (25)	1.4 (44)	+82	<0.001
FVC in liters (% of predicted)	2.2 (56)	2.8 (73)	+27	<0.05
TLC in liters (% of predicted)	8.5 (140)	6.6 (110)	-22	<0.001
RV in liters	5.9 (288)	3.6 (177)	-39	<0.001
Trapped gas in liters	2.4	1.2	-50	<0.001
Pao_2 in millimeters of mercury (room air)	64*	70		<0.05
$Paco_2$ in millimeters of mercury (room air)	40*	39		NS

FVC, Forced vital capacity; *TLC*, total lung capacity; *RV*, residual volume; *NS*, not significant.
*Two patients receiving oxygen excluded.

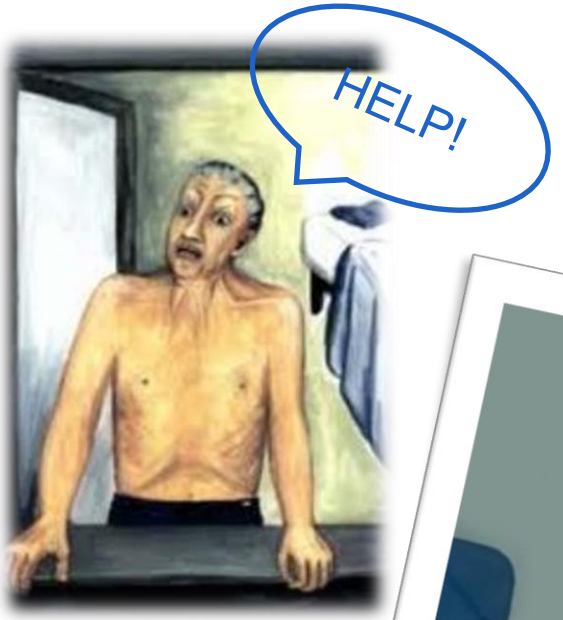
Lung Volume Reduction Surgery

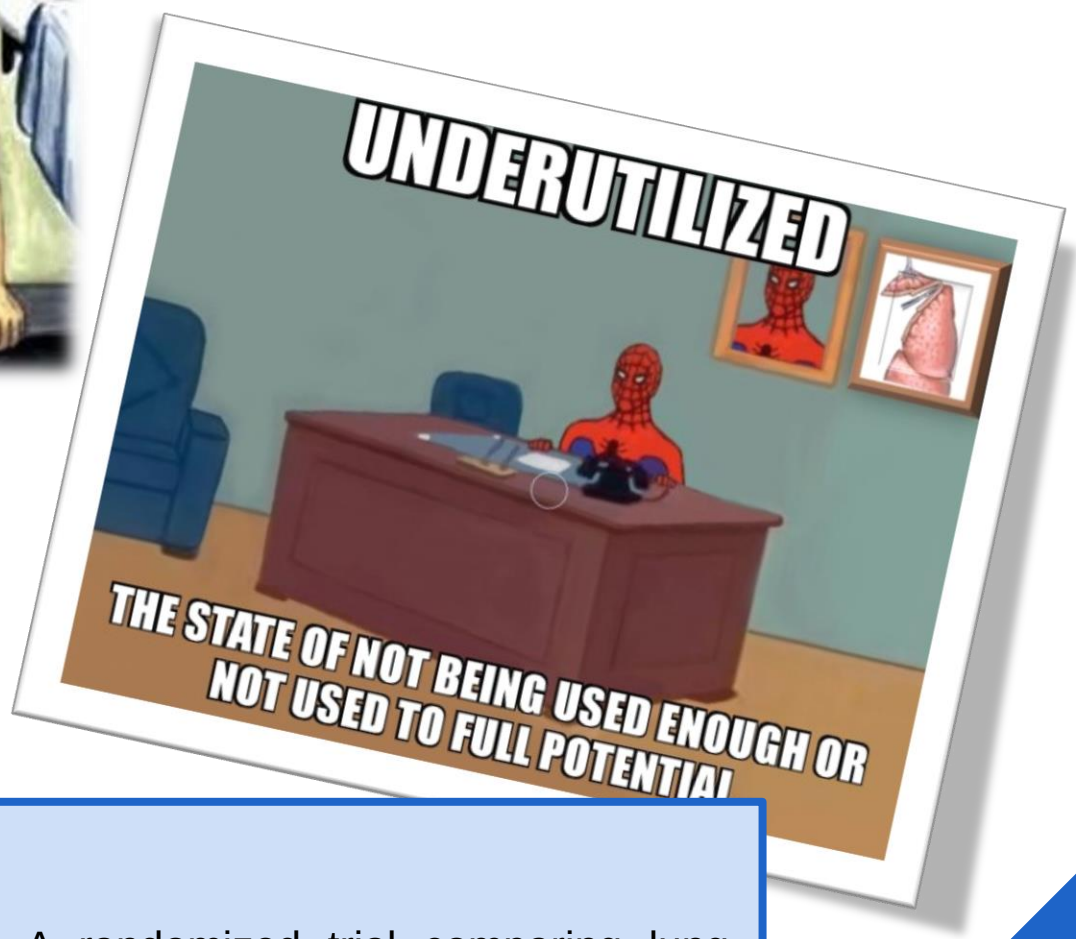
- 90’s : Many different trials
  - Randomized, Non Randomized,…
  - Improvement : FEV_1 – QoL – exercise capacity, walking distance
  - No data about improvement of survival

  - Rather high short time overall mortality : 16% - 19%

- Geddes D et al. Effect of lung-volume-reduction in patients with severe emphysema. *N Engl J Med* 2000;343:239-245
- Ferguson et al. Improved exercise performance following lung volume reduction surgery for emphysema. *Am J Respir Crit Care Med* 1998;157:1195–1203

LVRS controverse





- moeizame adoptie
- risicovolle chirurgie
- verwarring over effectiviteit en duurzaamheid
- complexe uitwerking
- onduidelijke selectiecriteria

- 2003 : NETT (Fishman et al)
  - National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume–reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;348:2059-2073

De NETT

The New England Journal of Medicine

VOLUME 345 OCTOBER 11, 2001 NUMBER 15

PATIENTS AT HIGH RISK OF DEATH AFTER LUNG-VOLUME–REDUCTION SURGERY

NATIONAL EMPHYSEMA TREATMENT TRIAL RESEARCH GROUP*

FEV1 ≤ 20% + homogeen emfyseem

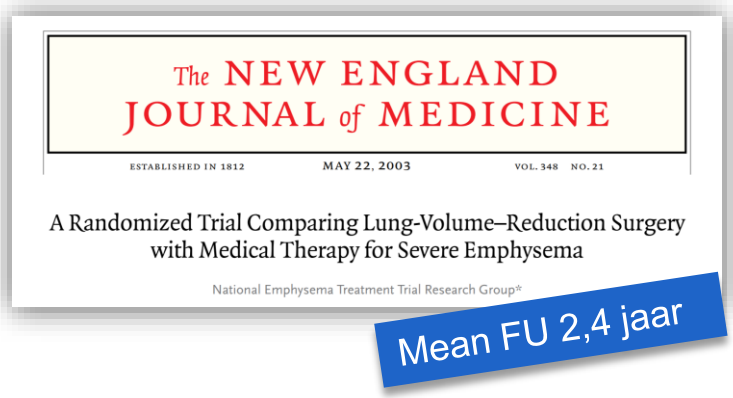
18% 30D mortaliteit na LVRS

FEV1 ≤ 20% + DLCO ≤ 20%

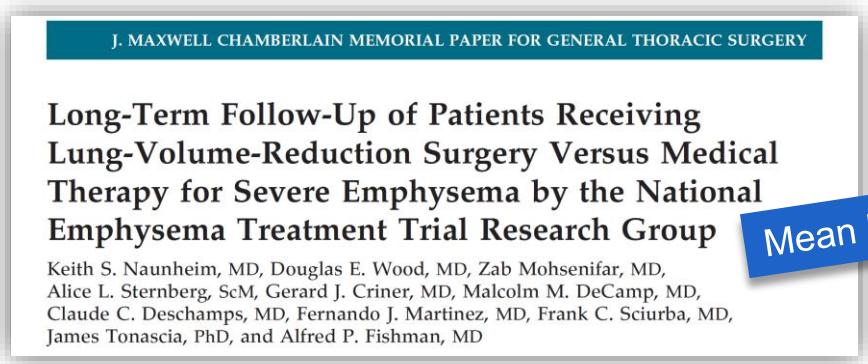
HOOG RISICO GROEP – EXCLUSIE VAN TRIAL

De NETT

1218 ptn gerandomiseerd
608 LVRS
610 Medische R/
140 high risk pre-exclusiegroep



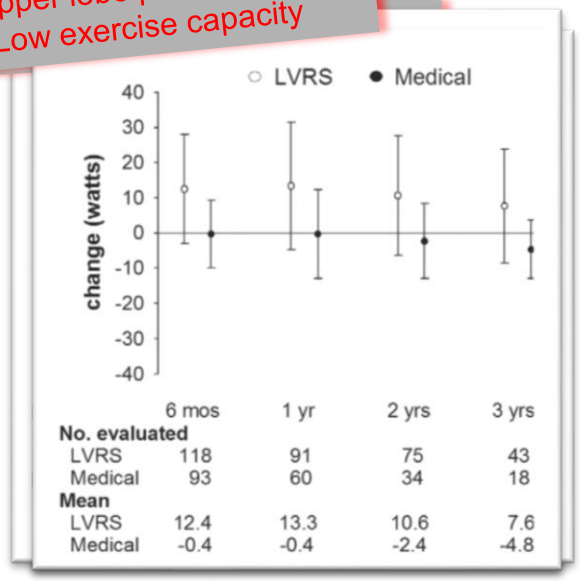
Mean FU 2,4 jaar



Mean FU 4,3 jaar

Ann Thorac Surg 2006;82:431-43

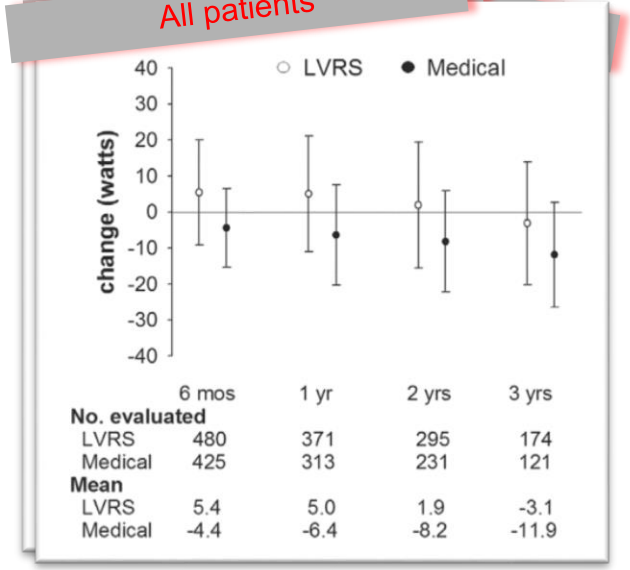
Upper lobe predominant
Low exercise capacity



- bij <u>geselecteerde</u> patienten met longemfyseem
- lagere lange termijn mortaliteit na LVRS
- toegename inspanningscapaciteit na LVRS
- toename levenskwaliteit – afname dyspnoeklachten
- in het bijzonder bij bovenkwabsemfyseem

  + lage preoperatieve inspanningscapaciteit
- LVRS niet aangewezen bij FEV1<20% en DLCO<20%
- 90d post-LVRS mortaliteit 5,2% (vs. 1,5%)
- 30d post-LVRS morbiditeit: cardiaal 20% - respiratoir 30%

All patients



Van NETT tot nu

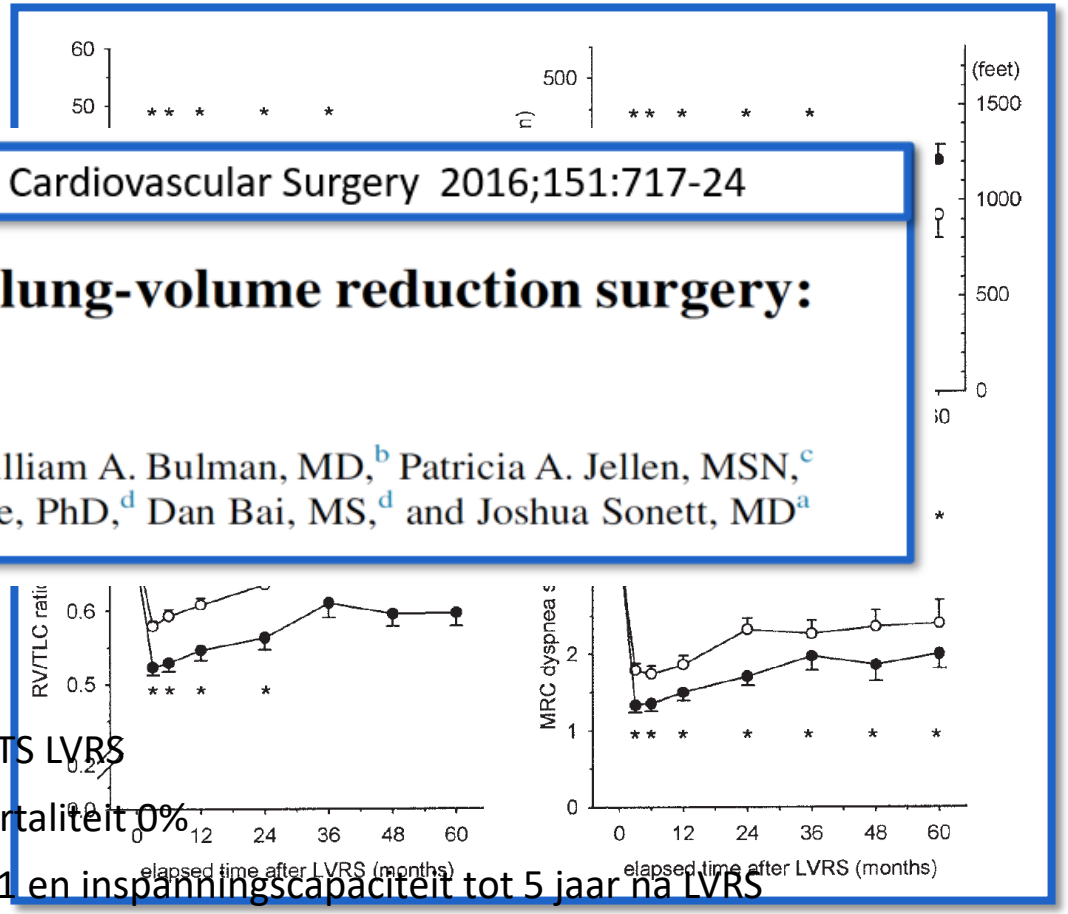
Persistent Benefit From Lung Volume

Ginsburg et al

The Journal of Thoracic and Cardiovascular Surgery 2016;151:717-24

The safety, efficacy, and durability of lung-volume reduction surgery: A 10-year experience

Mark E. Ginsburg, MD,[a] Byron M. Thomashow, MD,[b] William A. Bulman, MD,[b] Patricia A. Jellen, MSN,[c] Beth A. Whippo, MSN,[c] Cody Chiuzan, PhD,[d] Shing Lee, PhD,[d] Dan Bai, MS,[d] and Joshua Sonett, MD[a]



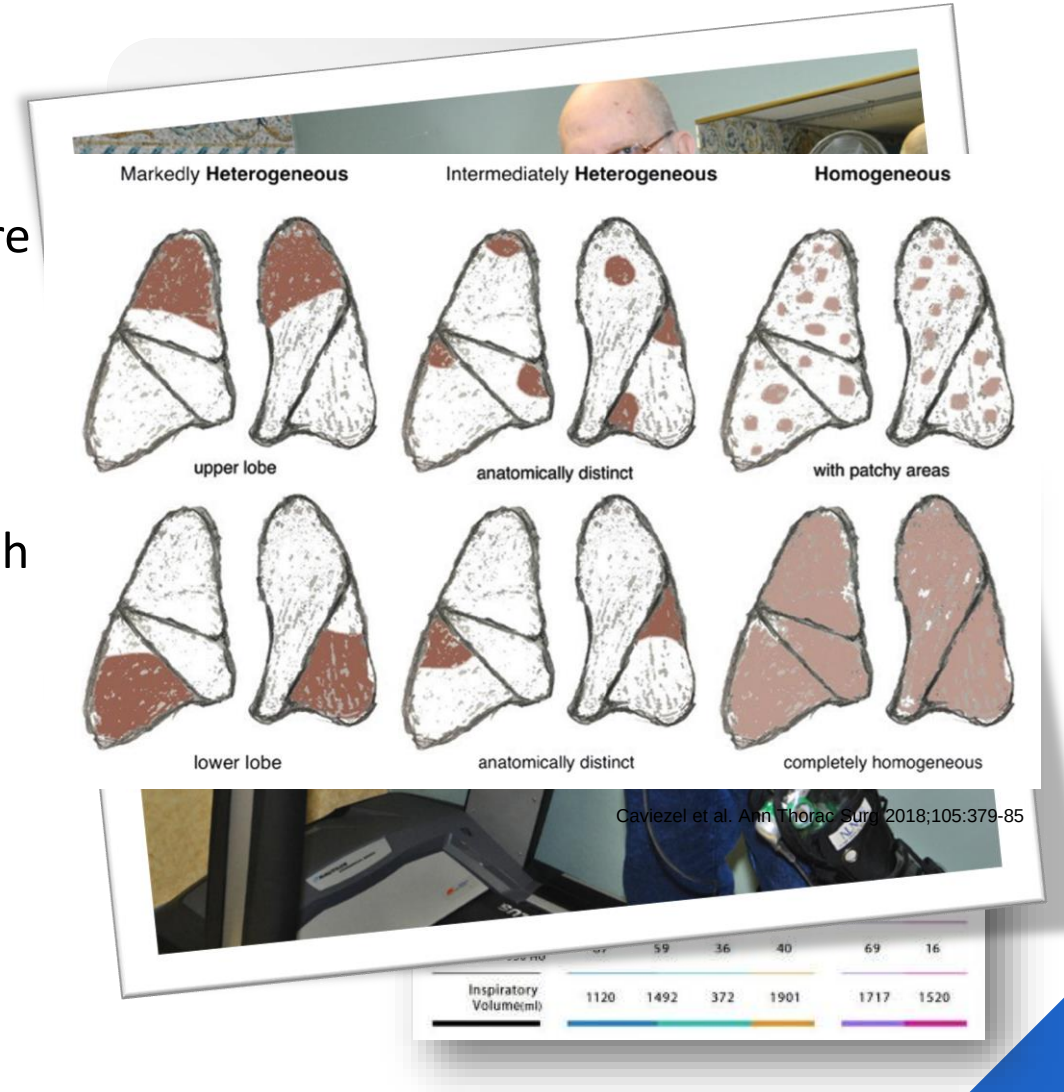
- n=250 138 homogeen(55%) 112 heterogeen (45%)
- Bilateral VATS LVRS
- 30d mortaliteit 2,4%
- 5jo (zonder LTX) 64% homogeen 73% heterogeen

- n=91
- bilaterale VATS LVRS
- 6-maand mortaliteit 0%
- Winst in FEV1 en inspanningscapaciteit tot 5 jaar na LVRS
- 5jo 78%

Operatief plan LVRS op maat van de patiënt

- bepalen resectievolume/gebied: CT, scintigrafie, software
- heterogeen emfyseem => volume: aangetast deel
- homogeen emfyseem => volume minder duidelijk
- berekening/inschatting volume ~spirometrie
- meestal bilateraal plan, bilaterale of unilaterale approach (2tijden)

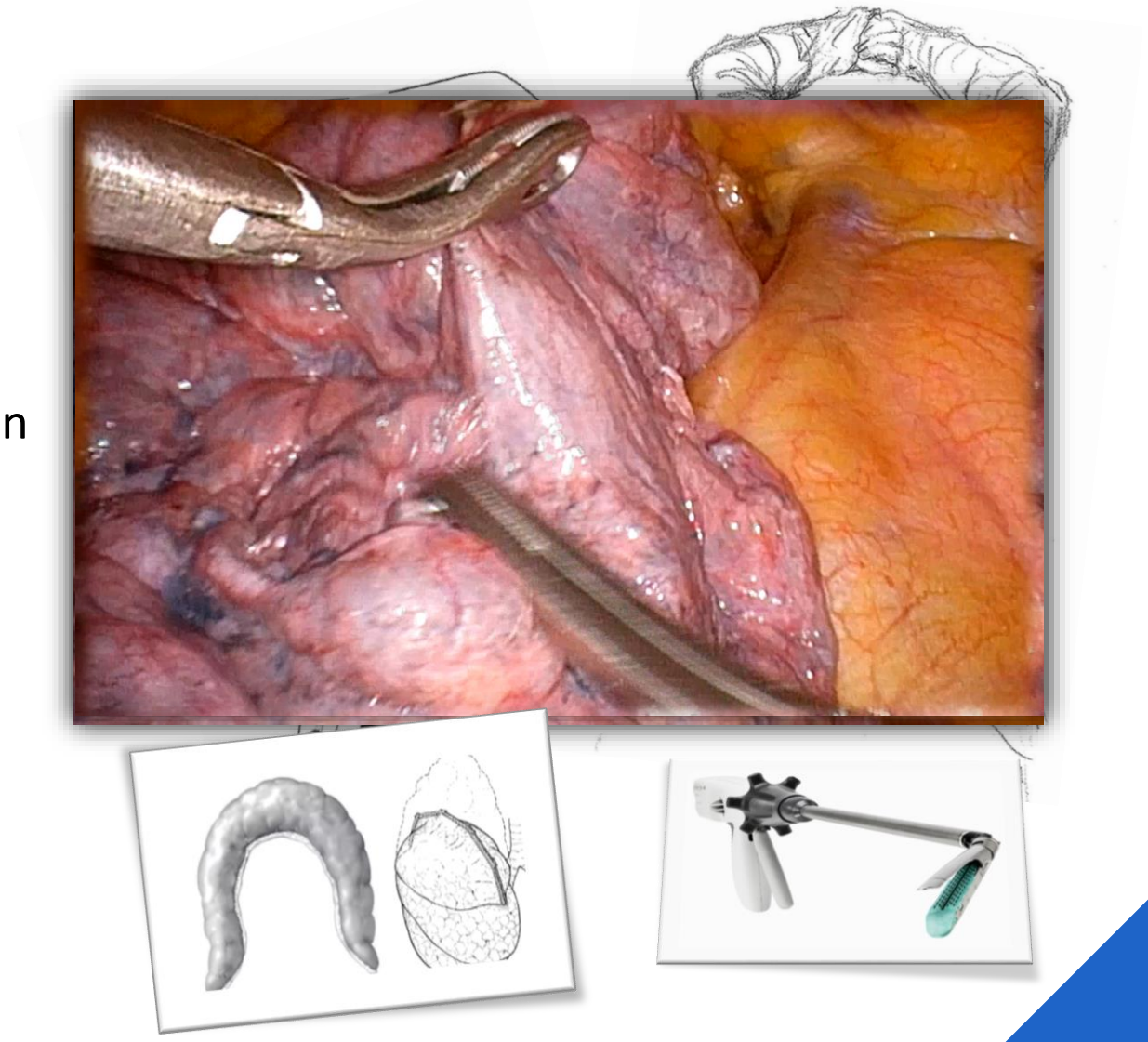
- planning ingreep bij herevaluatie na 6 à 10 weken **longrevalidatie**



Caviezel et al. Ann Thorac Surg 2018;105:379-85

Technische aspecten LVRS

- Video Assisted Thoracic Surgery
- losmaken ALLE verklevingen
- “shaping” resectie volume ~ operatief plan
- resectie longweefsel met staplers



Lung Volume Reduction Surgery

- In specific subgroup LVRS is benificial
- LVRS remains to have (high) peri-operative mortality and morbidity
- Most end stage COPD – emphysema pts
  - Homogeneous emphysema
  - Poor surgical candidates
- **Endobronchial lung volume reduction (ELVR)**
  - Strategies that minimize serious morbidity associated with LVRS appear attractive
  - Other physiology – based therapies

Endoscopic lung volume reduction (ELVR)

- Different techniques based on 2 different physiologic principles :

- Flow regulation and desuflation of hyper inflated areas
- Tissue compression and restoration of elastic recoil diminishing dynamic collaps

Ingenito EP, Wood DE, Utz JP. Bronchoscopic lung volume reduction in severe emphysema. *Proc Am Thorac Soc* 2008;5:454-460
Sahi H, Karnak D, Meli Y, et al. Bronchoscopic approach to COPD. *COPD* 2008;5:125-131

	Brand name	Type LVR	Firm	Mechanism	
Flow regulation	Exhale	Airway Bypass Stents	Broncus Technologies	Creation of extra-anatomic bronchial fenestration to deflate emphysematous lung parenchyma	Reversible
	RePneu	Lung Volume Reduction Coil (LVRC)	PneumRX	Pre-formed coil shape when delivered coils up and retracts diseased tissue thereby allowing expansion of healthier areas.	Irreversible
Lung Tissue Compression	Zephyr (Emphasys)	Endobronchial Valves (EBV)	PulmonX	One-way valve preventing air from entering in the blocked emphysematous segment, while allowing venting of expired gas and bronchial secretions, leading to atelectasis with subsequent reduction in lung volume.	Reversible
	Spiration	Intrabronchial Valves (IBV)	Olympus		
	Aeriseal	Emphysematous Lung Sealant (ELS)	Aeris	Tissue sealant which flows into the alveolar compartiment, polymerizes and seals target area. Gas in the sealed area is absorbed leading to volume reduction.	Irreversible
	InterVapor	Bronchoscopic Thermal Vapor Ablation (BTVA)	Uptake Medical	Heated water vapor to produce a thermal reaction leading to localized inflammatory response inducing fibrosis and atelectasis with subsequent reduction in lung volume.	

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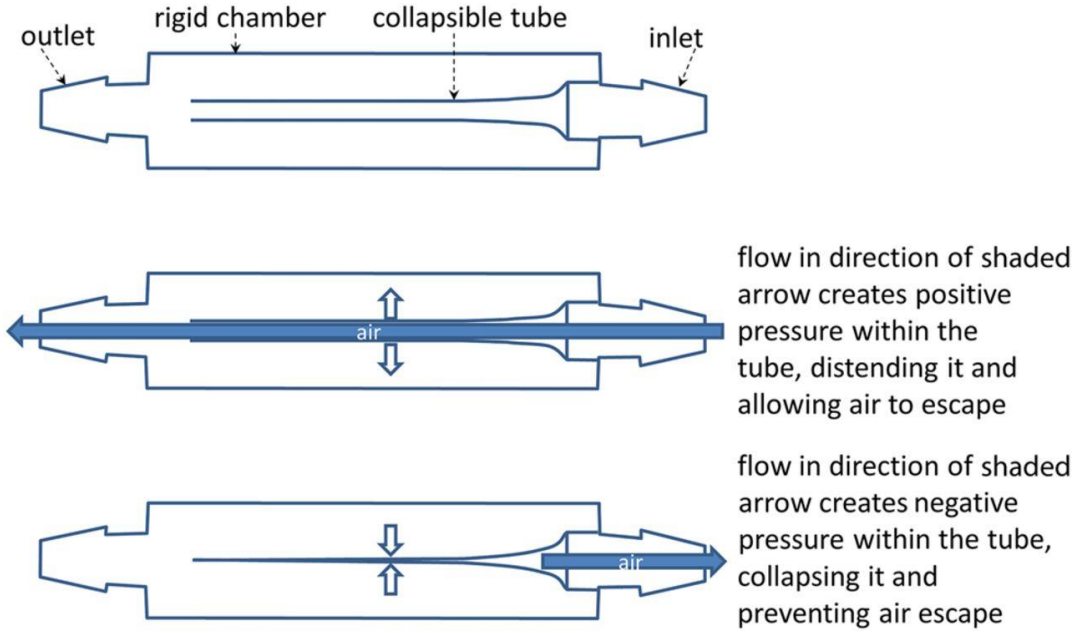
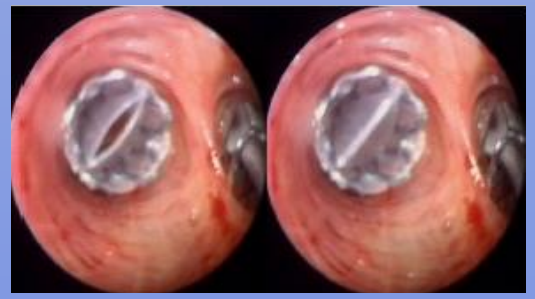
Endobronchial one-way valves

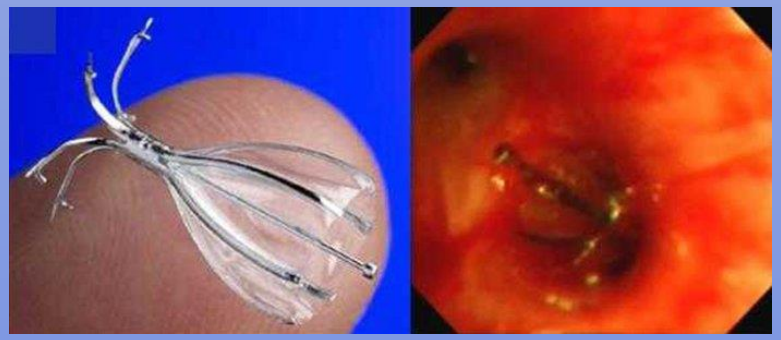
- One – way valves (‘Heimlich Valves) blocking bronchial lumina leading to targeted regions of emphysema :
  - Gas/air can vent from the isolated lung region during exhalation.
  - Preventing air from refilling the isolated lung segment during inhalation
  - Mucus can be expelled trough the valve



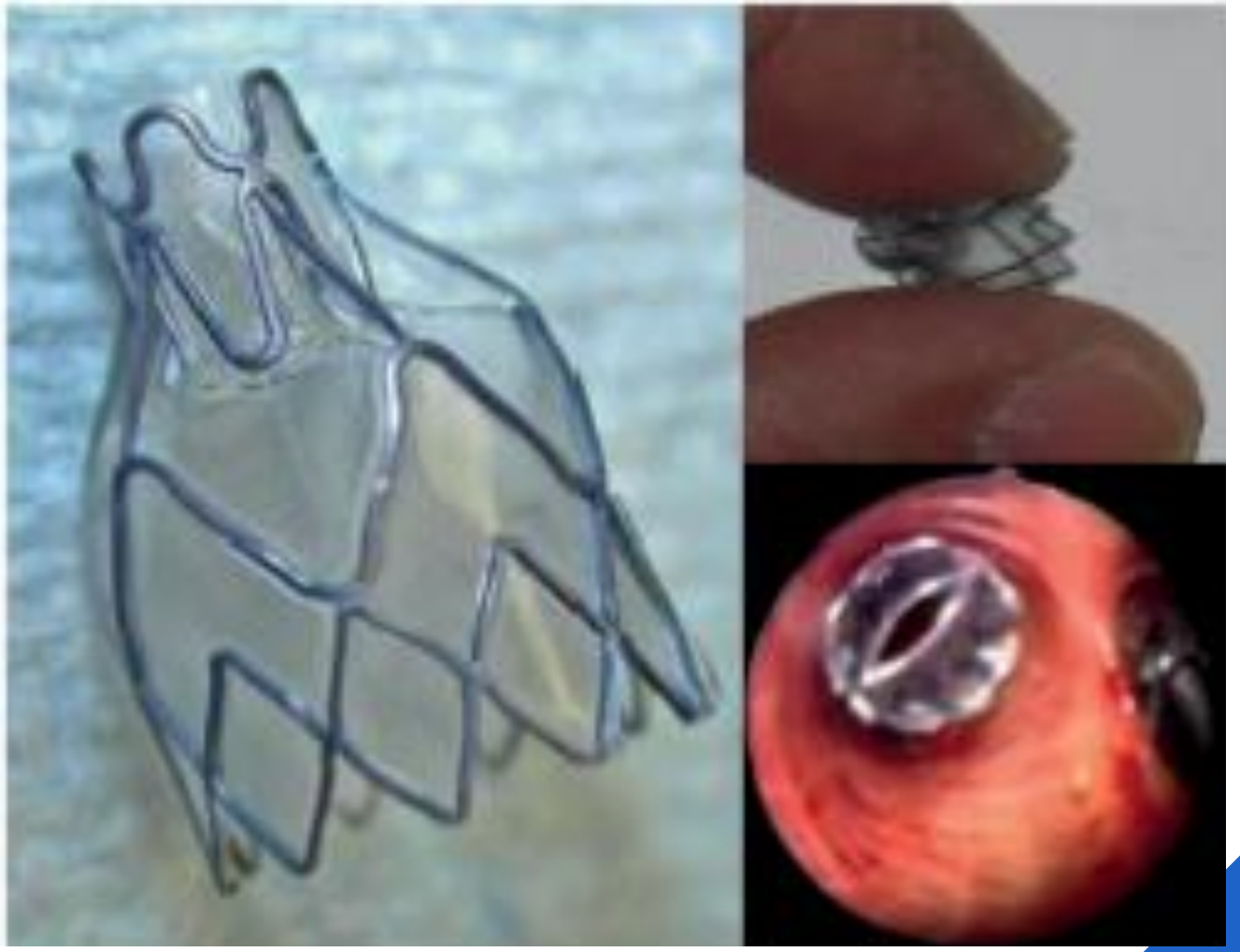
EBV



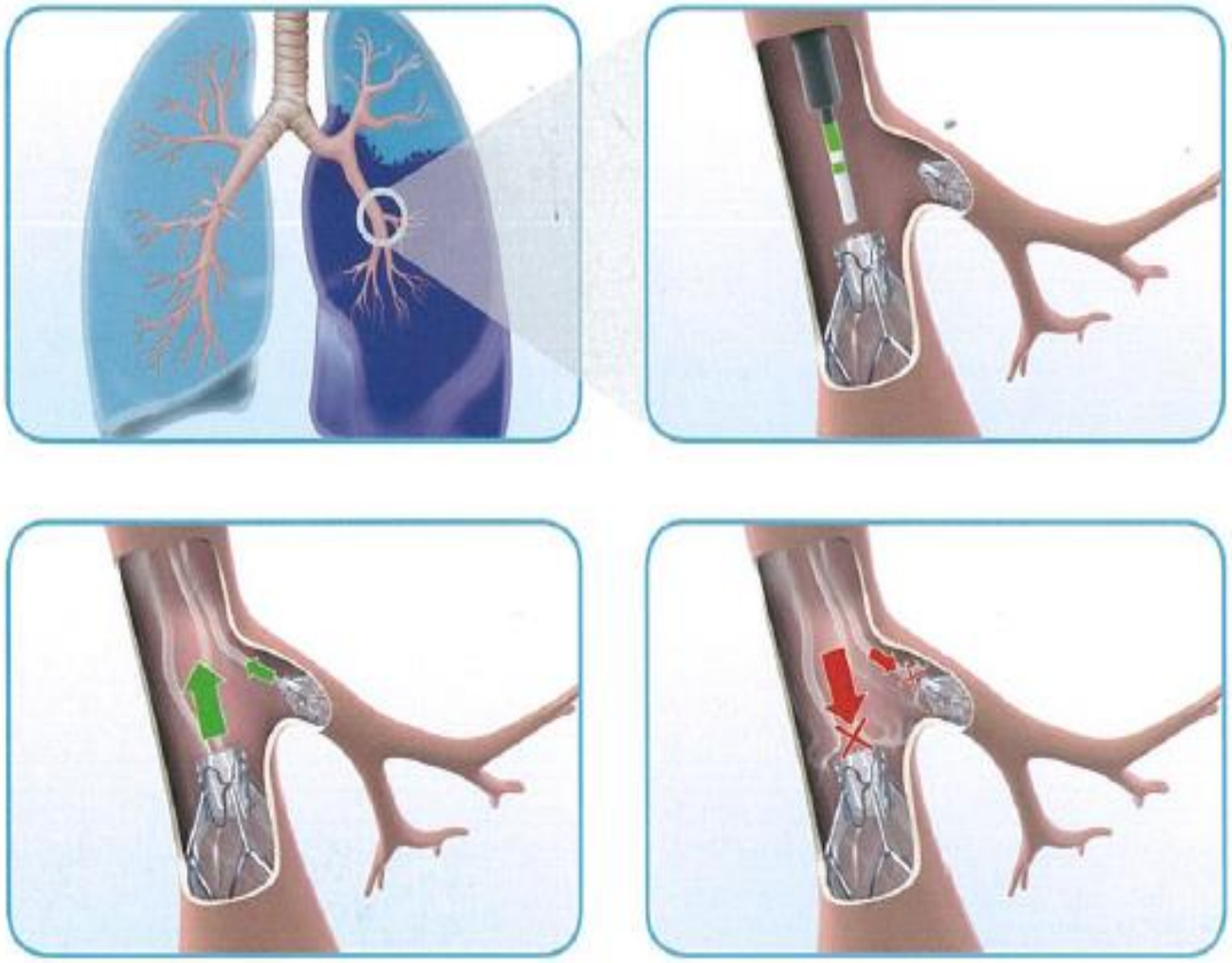
IBV



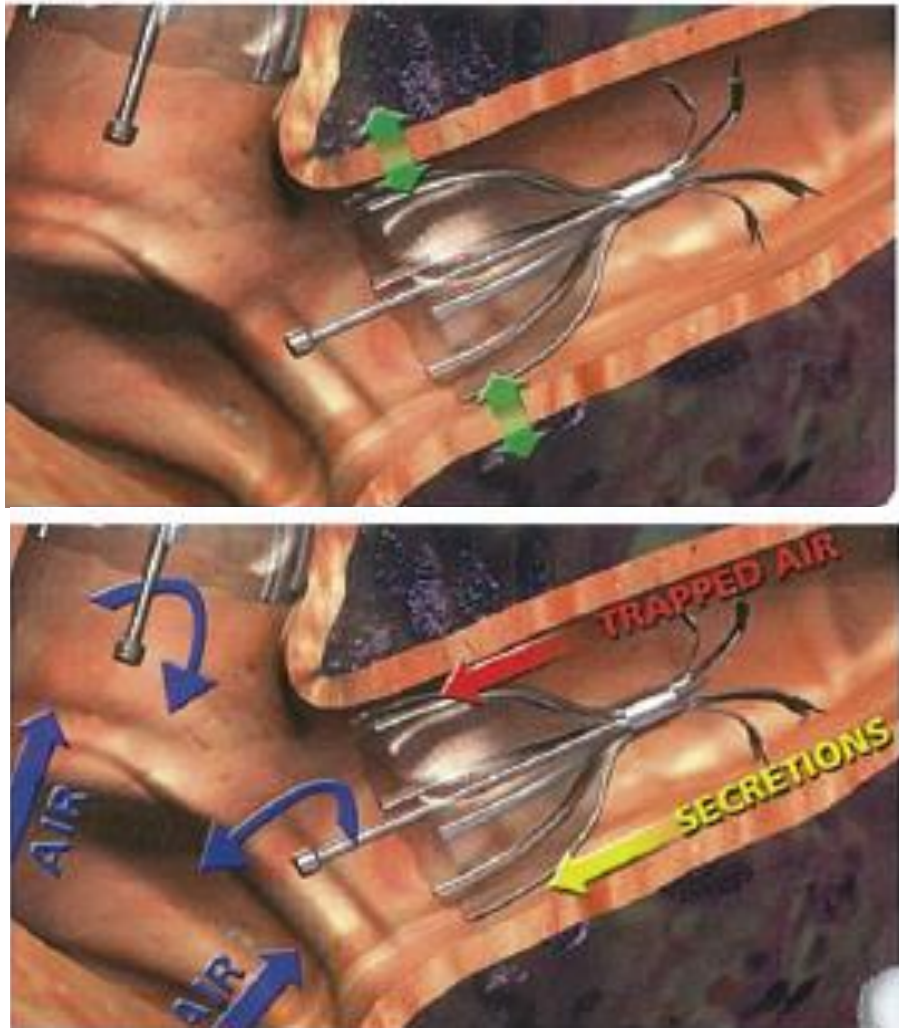
EBV - Zephyr - (PulmonX – previous Emphasys)
IBV - (Olympus – previous Spiration)



Endobronchial one-way valves : EBV - Zephyr



Endobronchial one-way valves : IBV - Olympus



Endobronchial one-way valves : EBV

ORIGINAL ARTICLE

A Randomized Study of Endobronchial Valves for Advanced Emphysema

Frank C. Sciurba, M.D., Armin Ernst, M.D., Felix J.F. Herth, M.D., Charlie Strange, M.D., Gerard J. Criner, M.D., Charles H. Marquette, M.D., Ph.D., Kevin L. Kovitz, M.D., M.B.A., Richard P. Chiacchierini, Ph.D., Jonathan Goldin, M.D., Ph.D., and Geoffrey McLennan, M.D., Ph.D., for the VENT Study Research Group*

- Endobronchial valve for emphysema palliation trial
- Randomized, prospective, multicentre study
  - Heterogeneous emphysema
  - 2:1 randomisation to receive therapy - unilateral treatment
  - Complete lobar occlusion
- Co-primary effectiveness endpoints
  - Percent change in FEV1
  - 6 MWD

Sciurba FC, Ernst A, Herth FJF, et al. A randomized study of endobronchial valves for advanced emphysema. *N Engl J Med* 2010;363:1233-1244 [US Vent]

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

Clinical Relevance?

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

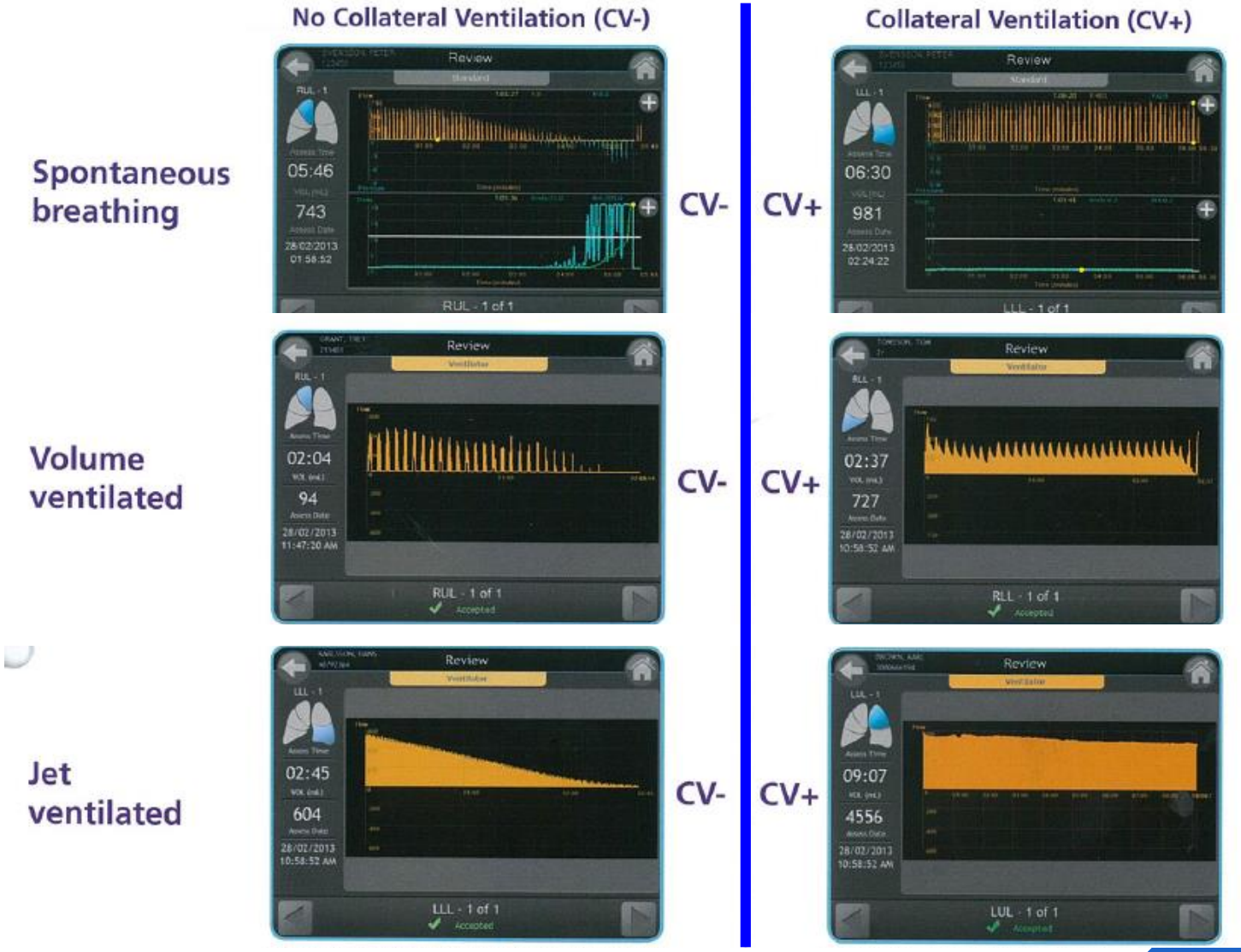
Endobronchial one-way valves
Rapport Kenniscentrum 2009

AANBEVELINGEN

Terugbetaling van [illegible] patiënten met longemfyse[illegible] terminale fase kan momenteel niet [illegible]und, omwille [illegible]nde aangetoond klinisch voordeel [illegible] en hoge kosten in verhouding tot een beper[illegible]aten kunnen een groter nut hebben bij subgroepen van [illegible]duidelijk hoe deze subgroepen kunnen worden geïd[illegible]mogelijke nadelen zou compenseren. [illegible]bepen aa[illegible]en prospectieve RCT met ondern[illegible]oriënteerde eindpunten.

Complete Fissures? Collateral Ventilation?

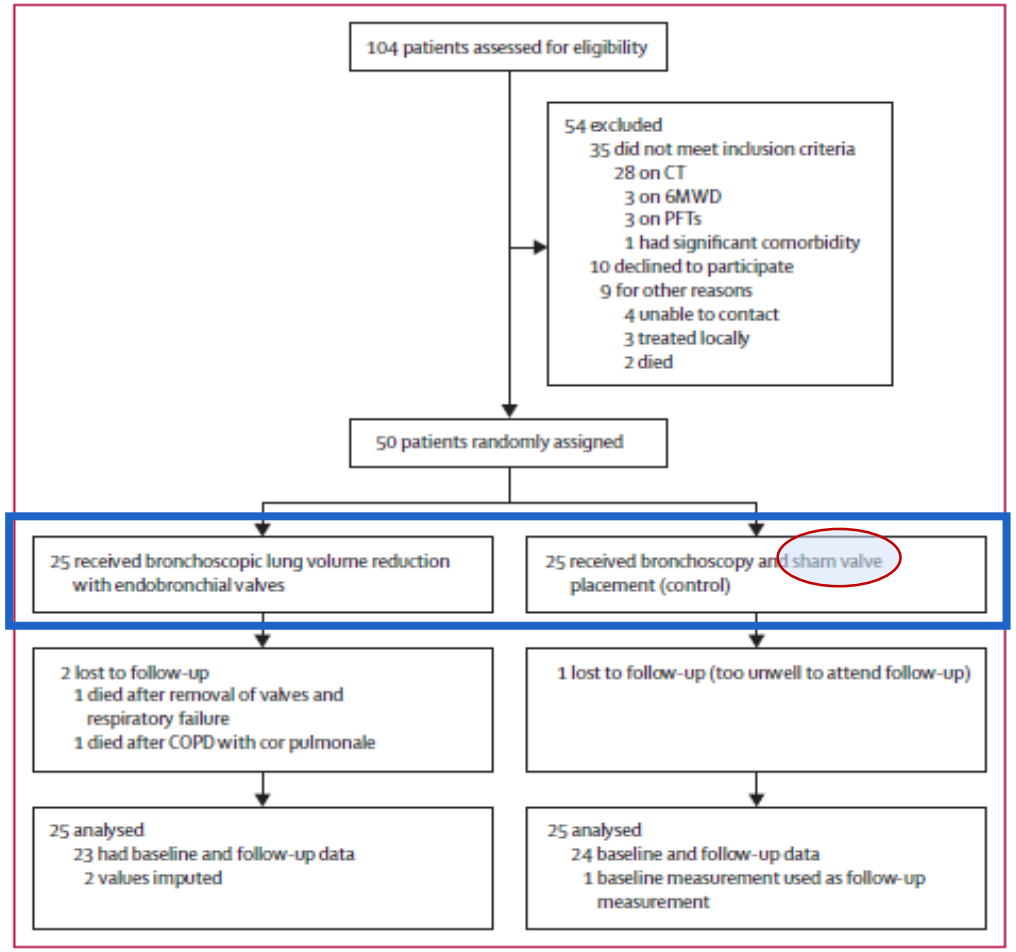
Predicting collateral ventilation by the chartis system.



Herth et al. Radiological and clinical outcomes of using ChartisTM to plan endobronchial valve treatment. *Eur Respir J* 2013;41:302-308

BELIEVER HIFI

Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial



	BLVR		Control (n=24)	p value*
	All (n=23)	CV-positive excluded (n=19)		
FEV_1	9 (39%)	--	1 (4%)	0·0044
>15% improvement	--	9 (47%)	1 (4%)	0·0022
RV	11 (48%)	--	7 (29%)	0·24
0·35 L reduction[20]	--	11 (58%)	7 (29%)	0·07
6MWD	12 (52%)	--	4 (17%)	0·012
26 m improvement[24]	--	12 (63%)	4 (17%)	0·004
Endurance cycle time	10 (43%)	--	2 (8%)	0·008
105 s improvement[23]	--	9 (47%)	2 (8%)	0·005
SGRQc	11 (48%)	--	11 (46%)	1·0
4 points reduction[21]	--	11 (58%)	11 (46%)	0·5
CAT	13 (57%)	--	7 (29%)	0·080
2 points reduction[22]	--	13 (68%)	7 (29%)	0·015

Data are n (%). CV-positive=collateral ventilation using Chartis system. BLVR=bronchoscopic lung volume reduction. FEV_1=forced expiratory volume in 1 s. RV=residual volume. 6MWD=6 min walking distance. SGRQc=St George's respiratory questionnaire for chronic obstructive pulmonary disease (COPD). CAT=COPD assessment test score. *Fisher's exact test (this analysis does not include imputed values).

Table 5: **Responder rates according to lung function, health status, and exercise criteria**

Lancet. 2015 Sep 12;386(9998):1066-73. doi: 10.1016/S0140-6736(15)60001-0. Epub 2015 Jun 23 – BeLieVeR-HIFI - Zoumot et al

STEVLIO

ORIGINAL ARTICLE

Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation

Karin Klooster, Nick H.T. ten Hacken, M.D., Ph.D., Jorine E. Hartman, Ph.D., Huib A.M. Kerstjens, M.D., Ph.D., Eva M. van Rikxoort, Ph.D., and Dirk-Jan Slebos, M.D., Ph.D.

- Randomized trial
- Patients with severe emphysema (Hom + Het)
- Confirmed absence of collateral ventilation
  - Chartis 
- Bronchoscopic endobronchial-valve treatment
- Continued standard medical care
- Primary outcomes (6 months)
  - Δ FEV_1
  - Δ FVC
  - Δ 6-minute walk distance.

IMPACT

Endobronchial Valve Therapy in Patients with Homogeneous Emphysema

Results from the IMPACT Study

Arschang Valipour[1], Dirk-Jan Slebos[2], Felix Herth[3], Kaid Darwiche[4], Manfred Wagner[5], Joachim H. Ficker[5], Christoph Petermann[6], Ralf-Harto Hubner[7], Franz Stanzel[8], and Ralf Eberhardt[3]; for the IMPACT Study Team*

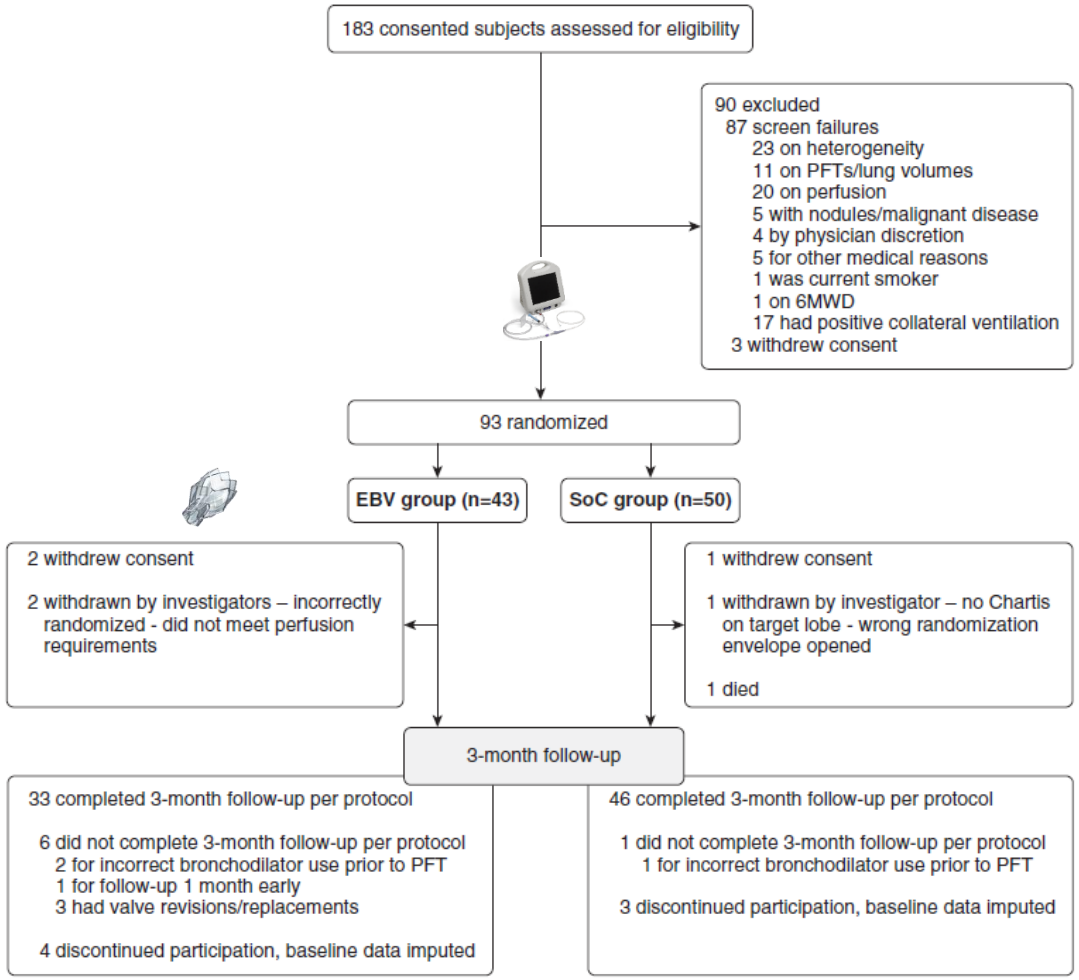


Table 3. Responders with Minimal Clinically Important Difference in Key Outcome Measures in Intention-to-Treat Population

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

Definition of abbreviations: 6MWD = 6-minute-walk distance; EBV = endobronchial valve; MCID = minimal clinically important difference; mMRC = modified Medical Research Council; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; SoC = standard of care.

*χ^2 test.

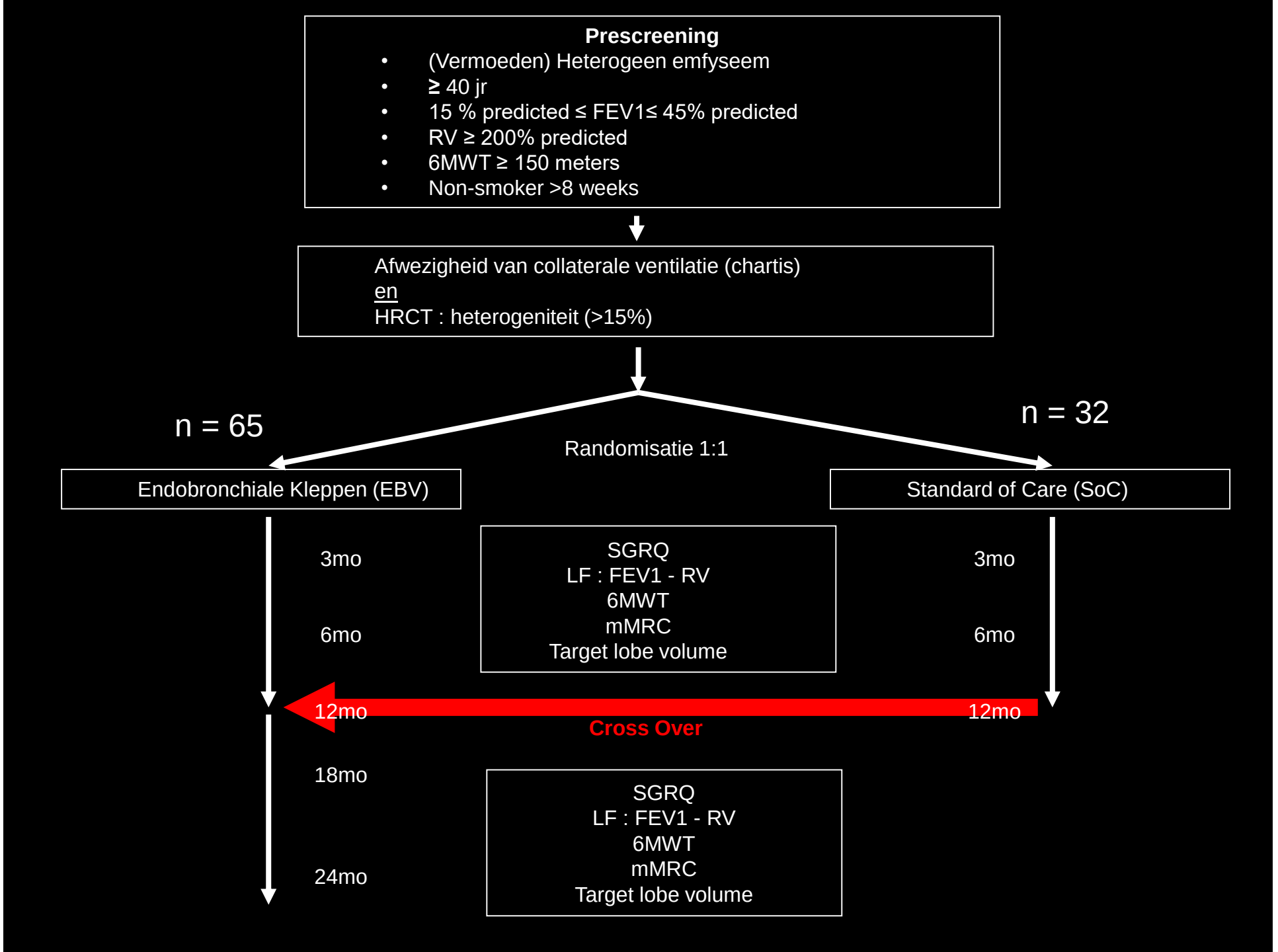
†FEV_1 responders were also evaluated using more conventional MCID thresholds of 10% and obtained similar results: greater than or equal to +10%: 40.5 versus 14.0% (EBV vs. SoC, respectively), $P = 0.004$.

IMPACT – Am J Respir Crit Care Med Vol 194, Iss 9, pp 1073-1082, nov 2016

TRANSFORM

A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM)

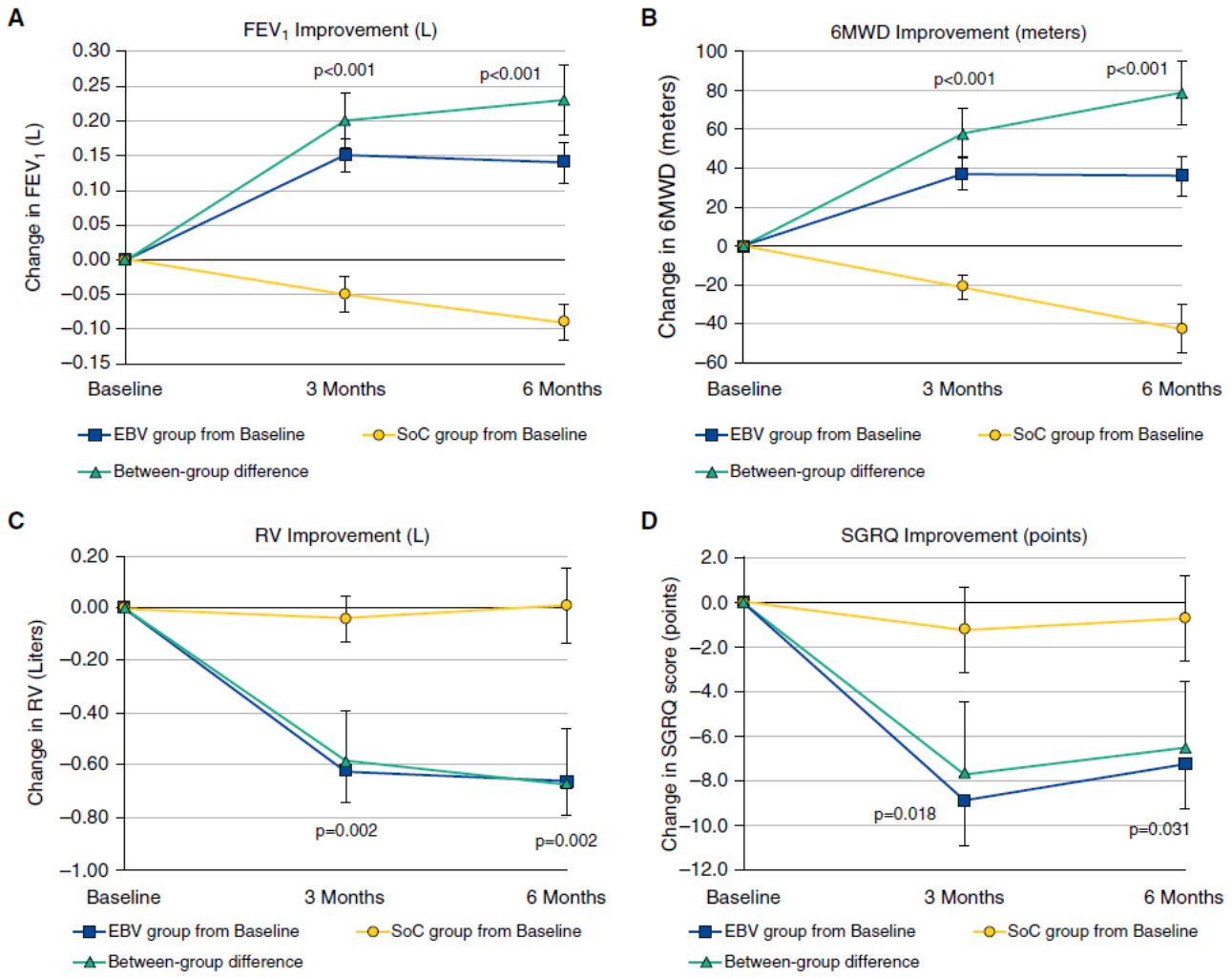
Samuel V. Kemp[1,2], Dirk-Jan Slebos[3], Alan Kirk[4], Malgorzata Kornaszewska[5], Kris Carron[6], Lars Ek[7], Gustav Broman[8], Gunnar Hillerdal[8], Herve Mal[9], Christophe Pison[10], Amandine Briault[10], Nicola Downer[2], Kaid Darwiche[11], Jagan Rao[12], Ralf-Harto Hübner[13], Christof Ruwwe-Glosenkamp[13], Valéry Trosini-Desert[14], Ralf Eberhardt[15], Felix J. Herth[15], Eric Derom[16], Thomas Malfait[16], Pallav L. Shah[1], Justin L. Garner[1], Nick H. ten Hacken[3], Hazem Fallouh[5], Sylvie Leroy[17], and Charles H. Marquette[17]; for the TRANSFORM Study Team*


Prescreening
(Vermoeden) Heterogeen emfyseem
≥ 40 jr
15 % predicted ≤ FEV1≤ 45% predicted
RV ≥ 200% predicted
6MWT ≥ 150 meters
Non-smoker >8 weeks
Afwezigheid van collaterale ventilatie (chartis)
en
HRCT : heterogeniteit (>15%)
n = 65
n = 32
Randomisatie 1:1
Endobronchiale Kleppen (EBV)
Standard of Care (SoC)
3mo
6mo
SGRQ
LF : FEV1 - RV
6MWT
mMRC
Target lobe volume
3mo
6mo
12mo
12mo
Cross Over
18mo
24mo
SGRQ
LF : FEV1 - RV
6MWT
mMRC
Target lobe volume

TRANSFORM

A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM)

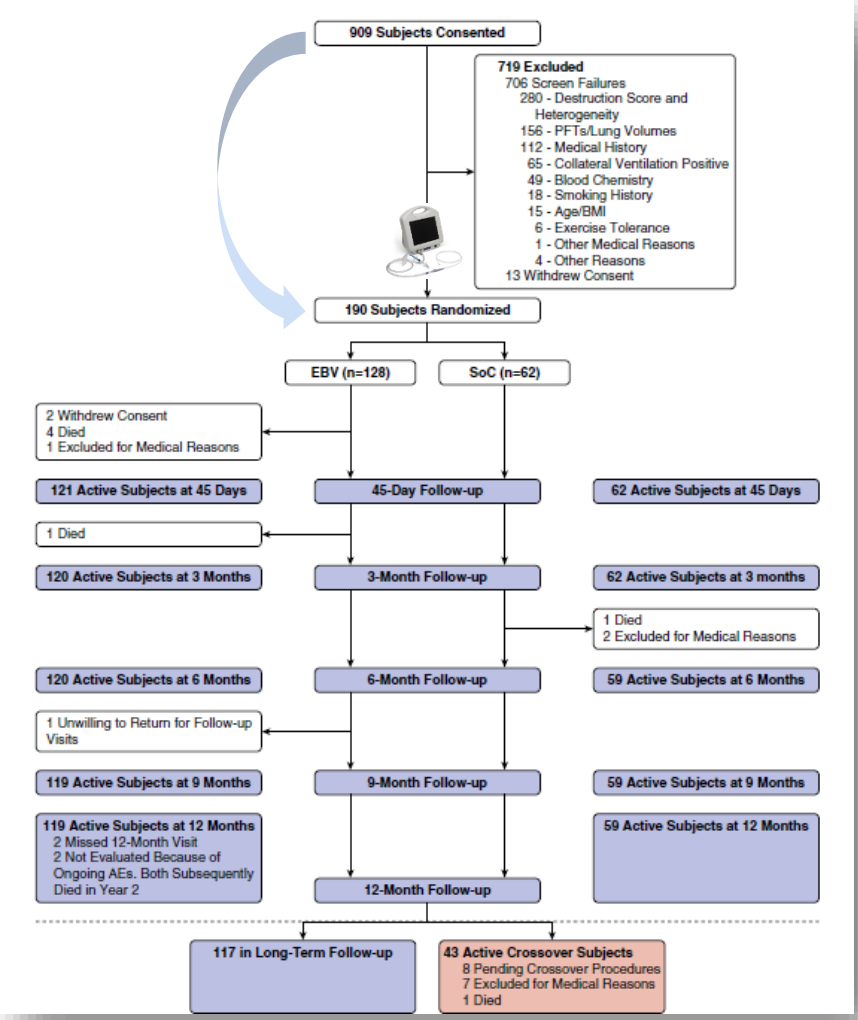
Samuel V. Kemp[1,2], Dirk-Jan Slebos[3], Alan Kirk[4], Malgorzata Kornaszewska[5], Kris Carron[6], Lars Ek[7], Gustav Broman[8], Gunnar Hillerdal[8], Herve Mal[9], Christophe Pison[10], Amandine Briault[10], Nicola Downer[2], Kaid Darwiche[11], Jagan Rao[12], Ralf-Harto Hübner[13], Christof Ruwwe-Glosenkamp[13], Valéry Trosini-Desert[14], Ralf Eberhardt[15], Felix J. Herth[15], Eric Derom[16], Thomas Malfait[16], Pallav L. Shah[1], Justin L. Garner[1], Nick H. ten Hacken[3], Hazem Fallouh[5], Sylvie Leroy[17], and Charles H. Marquette[17]; for the TRANSFORM Study Team*

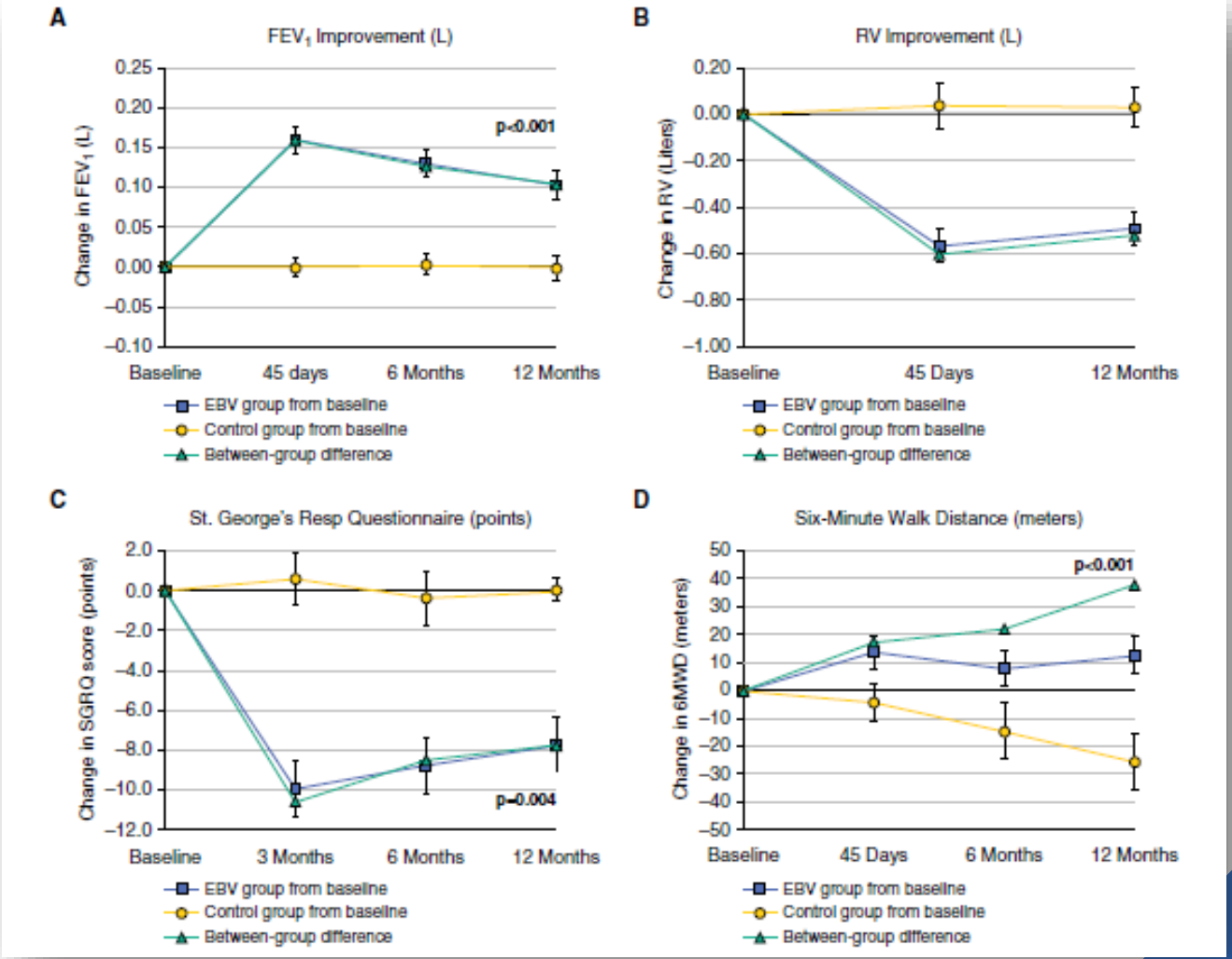


LIBERATE

A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE)

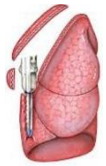
Gerard J. Criner[1], Richard Sue[2], Shawn Wright[2], Mark Dransfield[3], Hiram Rivas-Perez[4], Tanya Wiese[4], Frank C. Sciurba[5], Pallav L. Shah[6], Momen M. Wahidi[7], Hugo Goulart de Oliveira[8], Brian Morrissey[9], Paulo F. G. Cardoso[10], Steven Hays[11], Adnan Majid[12], Nicholas Pastis, Jr.[13], Lisa Kopas[14], Mark Vollenweider[15], P. Michael McFadden[16], Michael Machuzak[17], David W. Hsia[18], Arthur Sung[19], Nabil Jarad[20], Malgorzata Kornaszewska[21], Stephen Hazelrigg[22], Ganesh Krishna[23], Brian Armstrong[24], Narinder S. Shargill[25], and Dirk-Jan Slebos[26]; for the LIBERATE Study Group





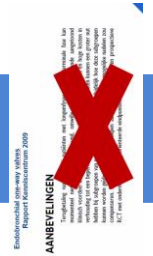
LIBERATE – Am J Respir Crit Care Med Vol 198, Iss9, pp 1151-1164, Nov 2018

NETT



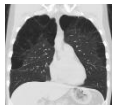
- Upper lobe
- Lower lobe
- Homogenous

Brompton Lancet Cohort



BeLieVeR

- Upper lobe
- Lower lobe



- Complete fissures
- (visual read)

TRANSFORM

- Upper lobe
- Lower lobe

- Heterogeneous
- No Collateral ventilaton (Chartis)

2001 2013 2014 2015 2016 2017 2018 2019 2020

NICE FDA RIZIV INAMI

VENT

- Upper lobe
- Lower lobe
- ?? Collateral Ventilation
- ?? Incomplete Occlusion

STELVIO

- Upper lobe
- Lower lobe

- Homogenous
- Heterogeneous
- No Collateral ventilaton (Chartis)

IMPACT

- Upper lobe
- Lower lobe

- Homogenous
- No Collateral ventilaton (Chartis)

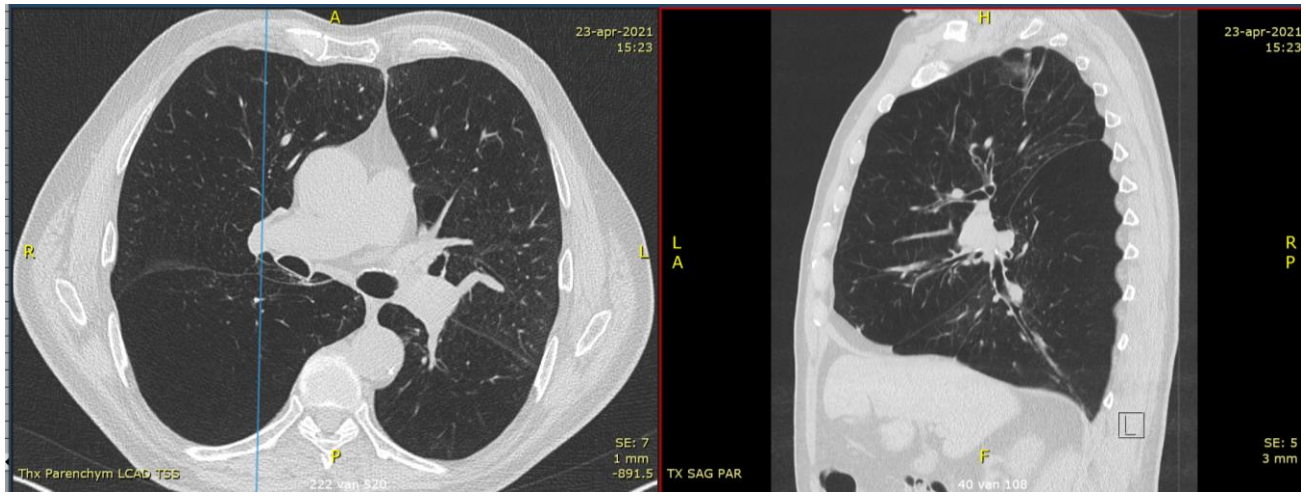
LIBERATE

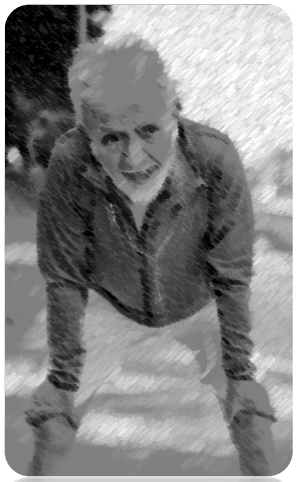
- Upper lobe
- Lower lobe

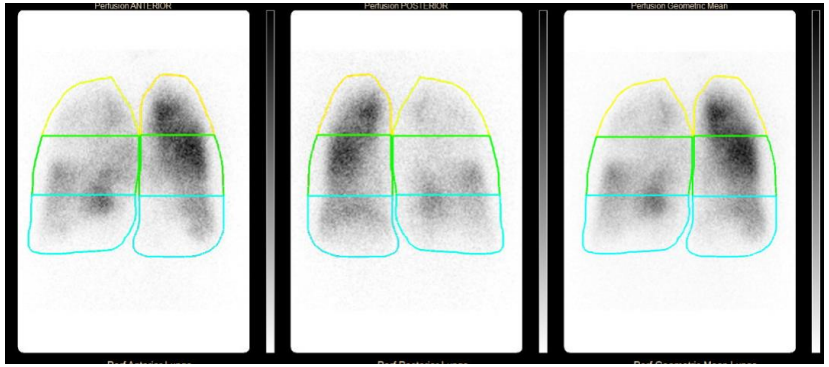
- Heterogeneous
- No Collateral ventilaton (Chartis)

 * Based on slide of P. Shah

		Pred	LL	Pre	%Pred
Spirometrie (Pred waarden GLI 2012)					
FVC	L	3.87	2.91	2.96	76
FEV 1	L	2.99	2.21	0.81	27
FEV 1 % FVC	%	77	65	27	
PEF	L/s	7.67	5.68	3.45	45
MFEF 75/25	L/s	2.45	1.13	0.23	10
MEF 75	L/s	6.82	4.00	0.37	5
PIF	L/s			4.10	
Fout ATS ERS 05				400	
Substantie					
Longvolumes (Pred waarden ERS 1993)					
VC_max	L	3.78	2.86		
VC	L	3.78	2.86	3.47	92
TLC He	L	6.34	5.19		
TLC Pleth	L	6.34	5.19	8.72	137
RV He	L	2.40	1.73		
RV Pleth	L	2.40	1.73	5.25	219
FRC-He	L	3.43	2.44		
ITGV	L	3.43	2.44	7.20	210
RV%TLC He	%	39.3	30.3		
RV%TLC Pleth	%	39.3	30.3	60.2	153







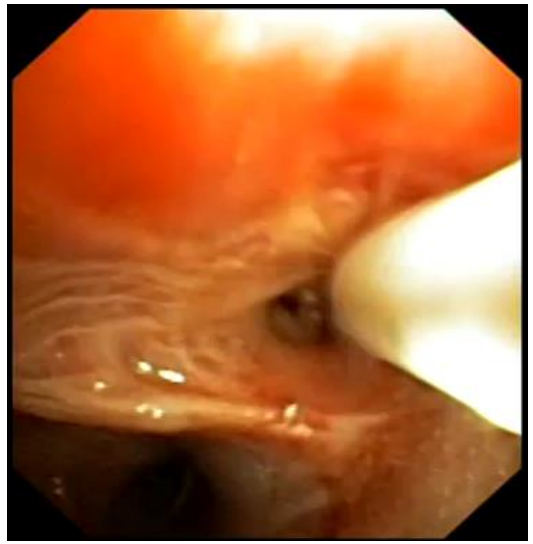
SUMMARY

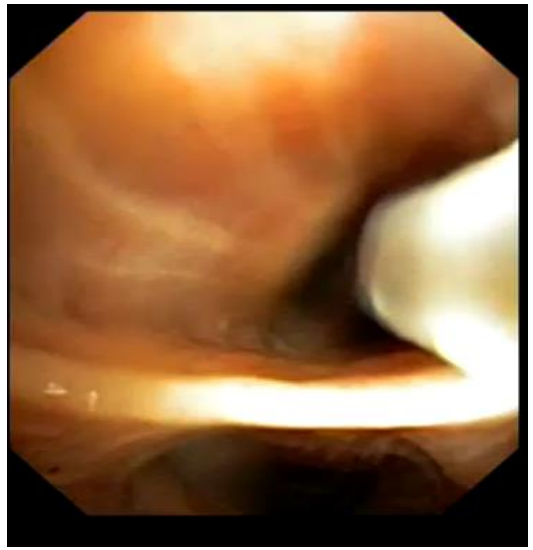
KEY

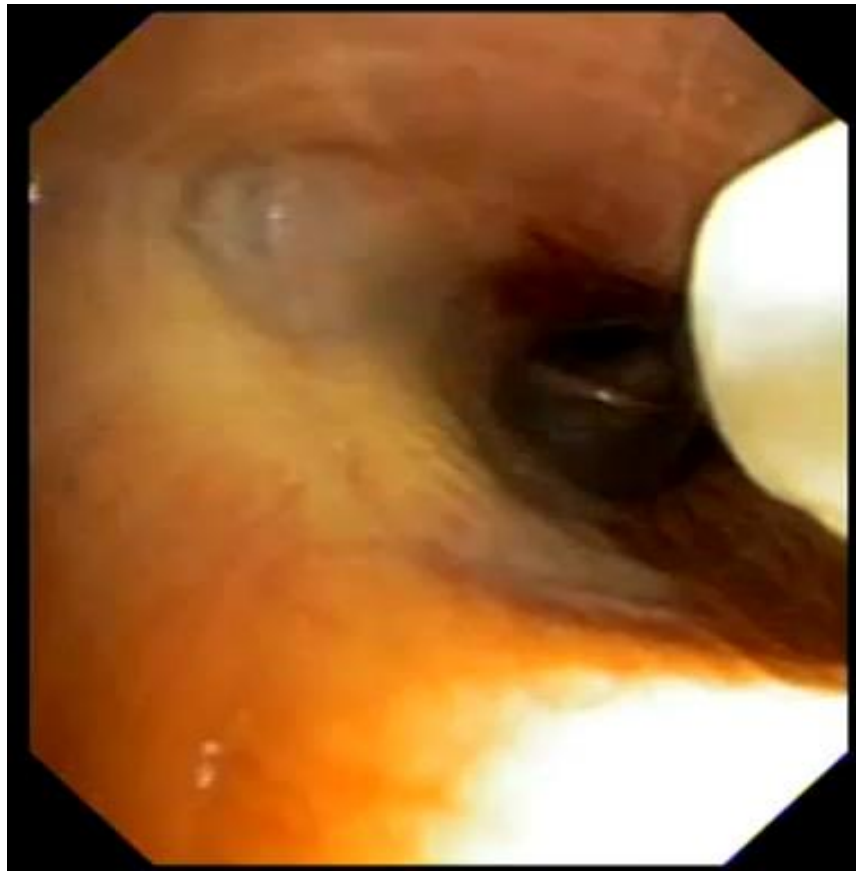
- ≥70% Voxel Density Less Than -910 HU
- 60-70% Voxel Density Less Than -910 HU
- 50-60% Voxel Density Less Than -910 HU
- <50% Voxel Density Less Than -910 HU
- ≥95% Fissure Completeness
- 80-95% Fissure Completeness
- <80% Fissure Completeness

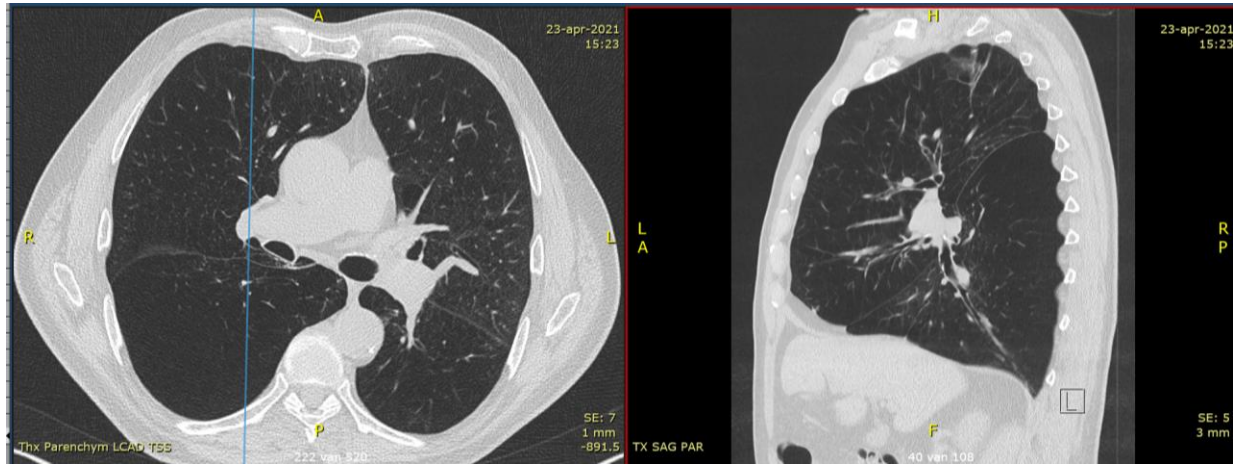
RESULTS

	RIGHT LUNG				LEFT LUNG	
	RUL	RUL+RML	RML	RLL	LUL	LLL
% Fissure Completeness	82.7	100.0	85.5	100.0	86.6	86.6
% Voxel Density Less Than -910 HU	74	72	69	76	62	53
% Voxel Density Less Than -950 HU	48	45	39	59	31	29
Inspiratory Volume (ml)	1689	2469	780	2055	2164	1302









		Pred	LL	Pre	%Pred
Spirometrie (Pred waarden GLI 2012)					
FVC	L	3.87	2.91	2.96	76
FEV 1	L	2.99	2.21	0.81	27
FEV 1 % FVC	%	77	65	27	
PEF	L/s	7.67	5.68	3.45	45
MFEF 75/25	L/s	2.45	1.13	0.23	10
MEF 75	L/s	6.82	4.00	0.37	5
PIF	L/s			4.10	
Fout ATS ERS 05				400	
Substantie					
Longvolumes (Pred waarden ERS 1993)					
VC_max	L	3.78	2.86		
VC	L	3.78	2.86	3.47	92
TLC He	L	6.34	5.19		
TLC Pleth	L	6.34	5.19	8.72	137
RV He	L	2.40	1.73		
RV Pleth	L	2.40	1.73	5.25	219
FRC-He	L	3.43	2.44		
ITGV	L	3.43	2.44	7.20	210
RV%TLC He	%	39.3	30.3		
RV%TLC Pleth	%	39.3	30.3	60.2	153

		Pred	LL	Pre	%Pred
Spirometrie (Pred waarden GLI 2012)					
FVC	L	3.85	2.89	3.68	96
FEV 1	L	2.97	2.19	0.95	32
FEV 1 % FVC	%	77	64	26	
PEF	L/s	7.67	5.68	3.25	42
MFEF 75/25	L/s	2.42	1.11	0.30	12
FEF 75	L/s	0.67	0.26	0.19	28
PIF	L/s			5.11	
Fout ATS ERS 05				400	
Substantie					
Longvolumes (Pred waarden ERS 1993)					
VC_max He	L	3.78	2.86	4.26	113
VC_max Plet	L	3.78	2.86	4.08	108
TLC He	L	6.34	5.19	7.69	121
TLC Pleth	L	6.34	5.19	7.69	121
RV He	L	2.40	1.73	3.44	143
RV Pleth	L	2.40	1.73	3.61	150
FRC-He	L	3.43	2.44	5.24	153
ITGV	L	3.43	2.44	5.97	174
RV%TLC He	%	39.3	30.3	44.7	114
RV%TLC Pleth	%	39.3	30.3	46.9	119

Terugbetaling Valves : welke patiënt?

De rechthebbende lijdt aan **longemfyseem** en voldoet, **na een traject van respiratoire revalidatie** en na een **optimale medicamenteuze behandeling**, conform de actueel geldende GOLD-aanbevelingen, aan onderstaande criteria:

- De rechthebbende lijdt aan **ernstig (GOLD III) tot zeer ernstig (GOLD IV) COPD**;
- De rechthebbende heeft een verminderde inspanningstolerantie **(6-MWT <450m)** ;
- De rechthebbende is beperkt in het dagelijks leven **(mMRC ≥2)** ;
- De rechthebbende heeft **minstens zes maanden voor de implantatie niet gerookt**, aangetoond door een **negatieve nicotine-detectietest** ;
- De te behandelen long vertoont een **hyperinflatie met een residueel volume>175% voor heterogeen emfyseem of een residueel volume >225% voor homogeen emfyseem**;
- De te behandelen lob heeft een intacte fissuur, aangetoond met een **fissuurintegriteit van minstens 95% op HRCT** OF de te behandelen lob heeft een semi-intacte fissuur (fissuurintegriteit tussen 80% en 95% op HRCT) waarbij de **afwezigheid van collaterale ventilatie kwantitatief** werd aangetoond.

Ernstig emfyseem (kliniek, longfunctie, evt beeldvorming)

RIZIV – Valves?

- GOLD III – IV
- 6-MWT <450m
- mMRC ≥2
- Rookstop > 6maand
- RV > 175% / RV > 225%
- Revalidatie (wensen) te volgen

Chirugie?

- Bullae
- Intralobaire Heterogeniteit
- Lage inspanningscapaciteit
- mMRC ≥2
- Rookstop > 6maand
- Hoog RV%TLC
- Revalidatie (wensen) te volgen

No Go?

- Frequent Exacerbators
- Small airway disease
- Pulmonale Hypertensie
- Respiratoire Insufficiëntie
- Actief rokend
- Geen revalidatie
- Geen motivatie

Ernstig emfyseem (kliniek, longfunctie, evt beeldvorming)

Kwalitatieve CT Thorax (geen contrast)

Aanvullend vragenlijsten, 6-MWT, perfusiescan, arteriële bloedgaswaarden en echocardiografie

Emfyseem MDO

- Destructie > 30 %
  - (HU -950) (min 1 lob)
- RV >175% - RV > 225%

LVR Chirurgie

Geen indicatie
Andere Therapie
Studie
Long Tx

- Fissuur > 95%

- Fissuur 80 – 95%

Collaterale Ventilatie
- Chartis +

Endoscopische LVR
Valves

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