Endoscopie interventionnelle dans la BPCO

Comment et pour qui ?

Colloque Médical du Jeudi, 22-11-2018

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Relations d'intérêts Christophe Pison

- **Type d'aides et champs**
  - **Au Pr. Ch. Pison pour déplacemetns inscriptions congrès *via* honoraires**
  - **CHUGA, recherche clinique *via* contrat unique**
  - **BPCO, asthme, hypertensions pulmonaires, transplantation, endoscopie interventionnelle, réhabilitation respiratoire, nutrition**

- **CHUGA, essais phase 2, 3 et 4 et dispositifs médicaux**
  - **Actélion**
  - **Astra Zeneca**
  - **Bayer**
  - **Boehringer Ingelheim**
  - **Chiesi**
  - **Gilead**
  - **GlaxoSmithKline**
  - **Lilly**
  - **Novartis**
  - **Pfizer**
  - **Stallergènes**
  - **Roche**

  - **Thérakos, PneumRx, PulmonX, Nuvaira**
  - **AGIRàDom, Vitalaire, Orkyn, SOS Oxygène**

Relations d'intérêts Amandine BRIAULT

- **Supports et domaines d'activité**
  - Invitations réunions médicales, honoraires pour interventions FMC, Proctor PulmonX
  - Essais cliniques, contrat unique
  - BPCO, Asthme, HTPs, Transplantation, Réhabilitation, Endoscopie

- **Industrie pharmaceutique**
  - Actélion
  - Astra Zeneca
  - Boehringer Ingelheim
  - GlaxoSmithKline
  - Novartis
  - Pfizer
  - Chiesi

- **Dispositifs médicaux et soins à domicile**
  - PneumRx, ABS-Bolton, Holaira, Novatech, PulmonX
  - AGIR@dom, Vitalaire, Linde

Sommaire

- **BPCO – recommandations GOLD 2019**

- **Techniques endoscopiques**
  - **valves**
  - **coils**
  - **vapeur**
  - **dénervation ciblés des poumons, DCP**

- **Paysage en 2018-2019**

Global Initiative for Chronic
Obstructive
Lung
Disease

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD Definition

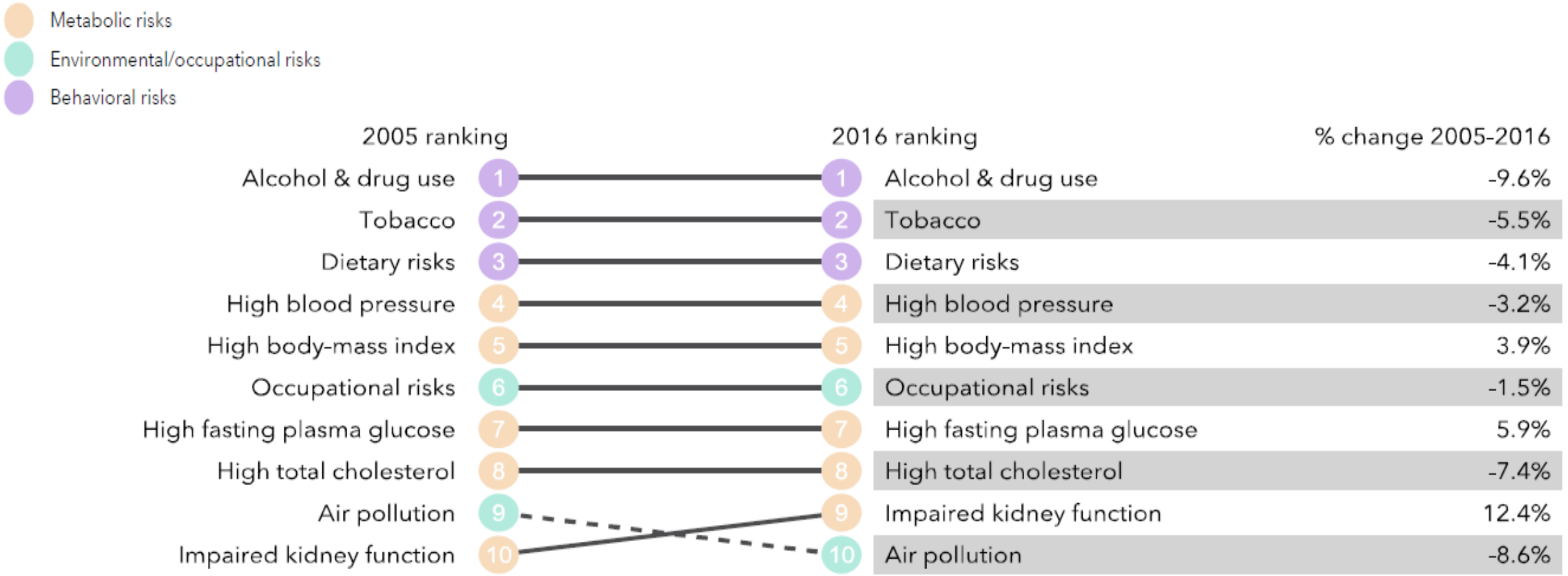
- Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

Chronic Obstructive Pulmonary Disease (COPD)

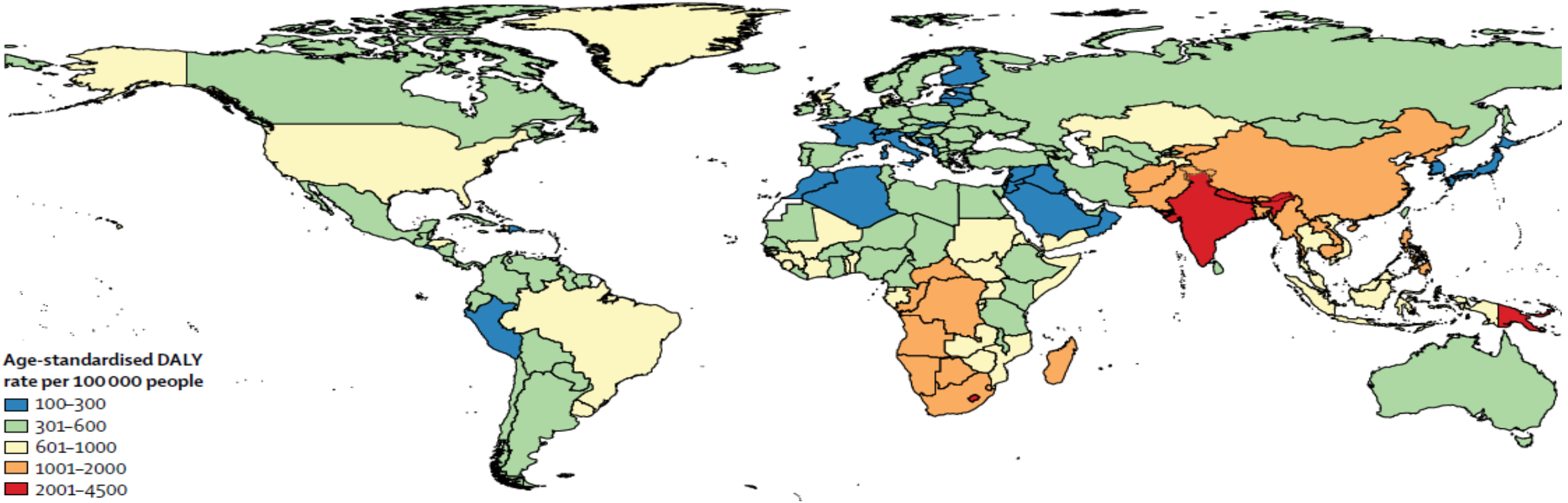
- COPD is currently the fourth leading cause of death in the world.[1]
- COPD is projected to be the 3rd leading cause of death by 2020.[2]
- More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally.
- Globally, the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and aging of the population.

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**(9859): 2095-128.
2. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006; **3**(11): e442.

Facteurs de risques de la plupart des décès et handicaps en France entre 2005 et 2016



Worldwide Burden of COPD by 2015

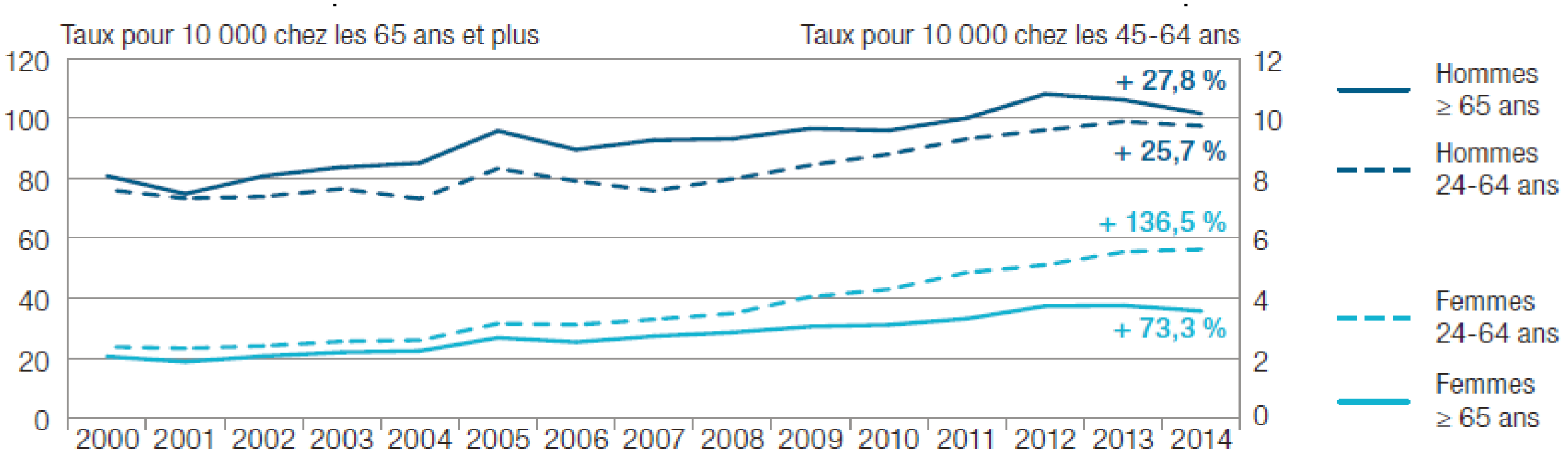


- Age-standardized DALY, disability-adjusted life years, rate per 100 000 people

- Increase prevalence of 44.2% between 1995 and 2015, 174.5 millions individuals, decrease prevalence of 14.7% in age-standardized prevalence, 3.2 million people died

GBD 2015 Chronic Respiratory Disease Collaborators, *Lancet Respiratory Medicine 2017; on line August 16*

Burden of COPD in France by 2014



- Trends of hospitalization rate for exacerbation / year per 10 000 people according to gender and age.
  Etat de la Santé et de la Population France, 2017, DRESS, p. 266

Smoking in Europe, Women

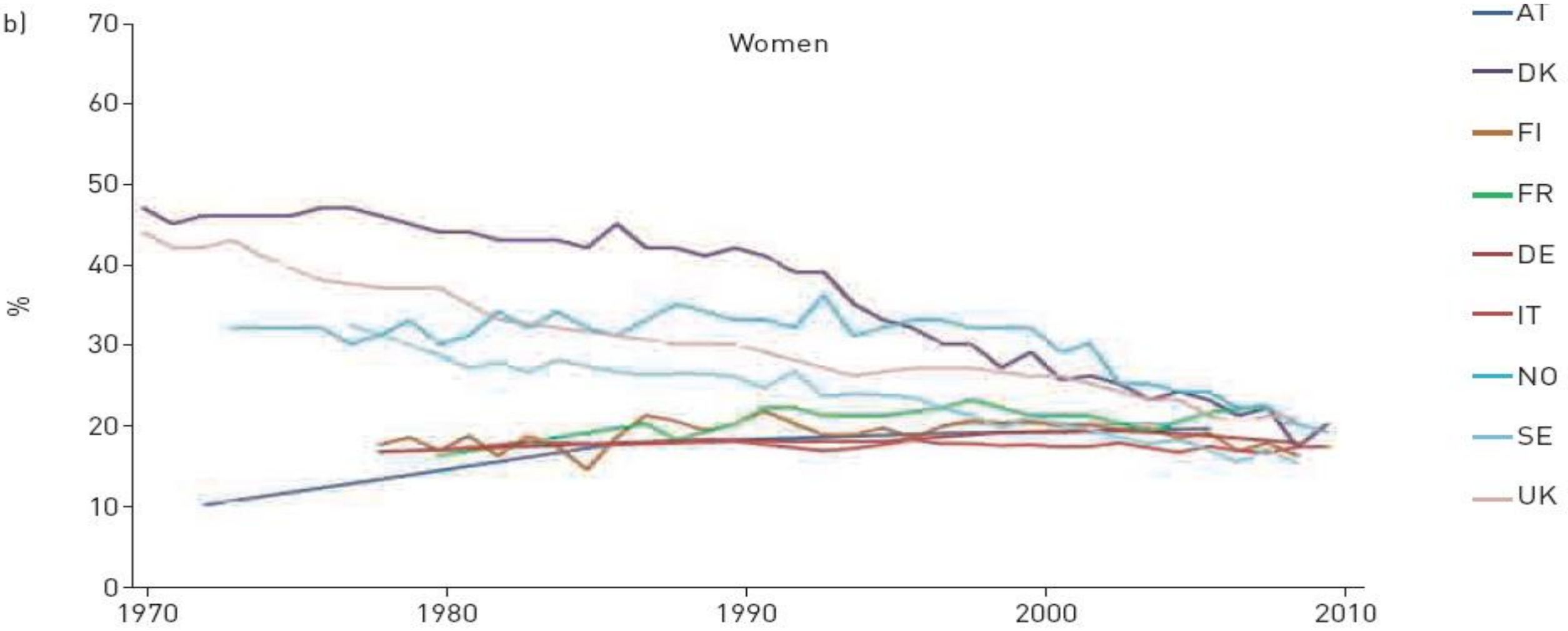


Figure 10 – Trends in daily smoking prevalence among a) men and b) women in selected countries, 1970-2010. Source: Organisation for Economic Co-operation and Development StatExtracts.

Smoking in Europe, Men

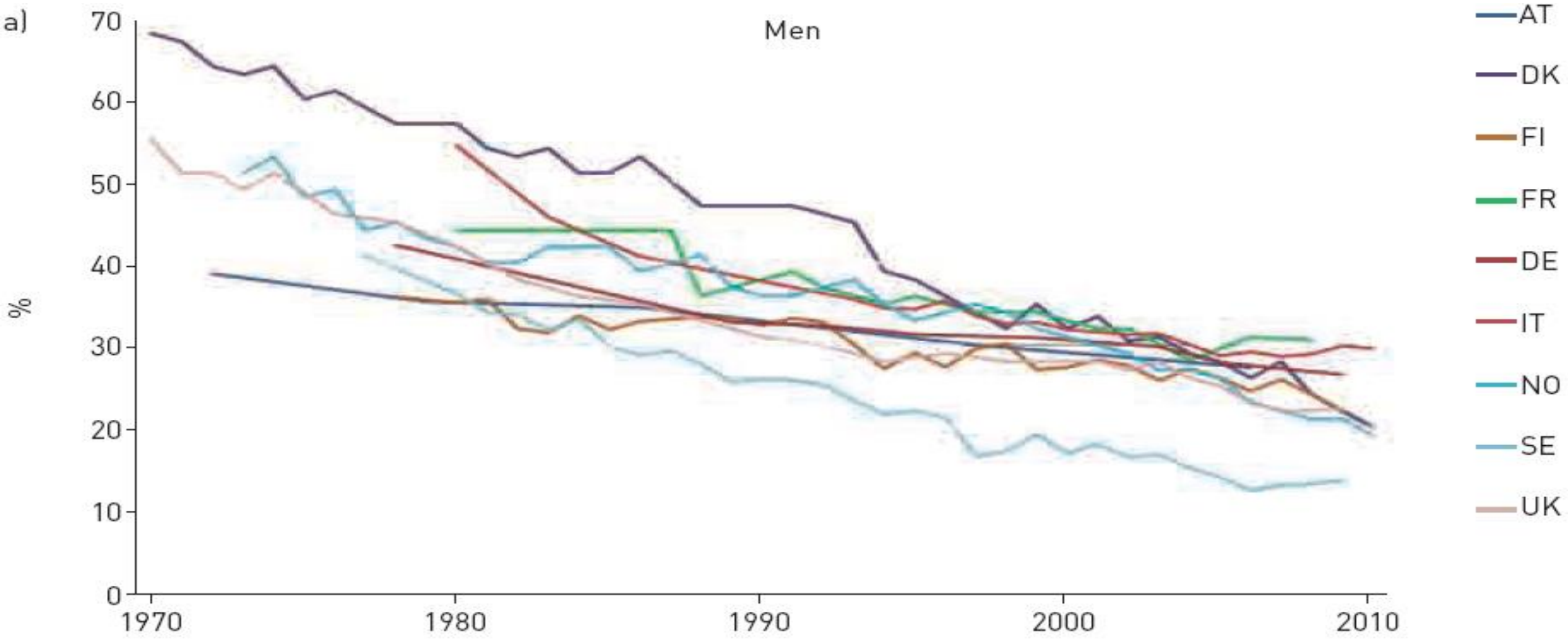


Figure 10 – Trends in daily smoking prevalence among a) men and b) women in selected countries, 1970-2010. Source: Organisation for Economic Co-operation and Development StatExtracts.

Etiology, pathobiology & pathology of COPD leading to airflow limitation & clinical manifestations

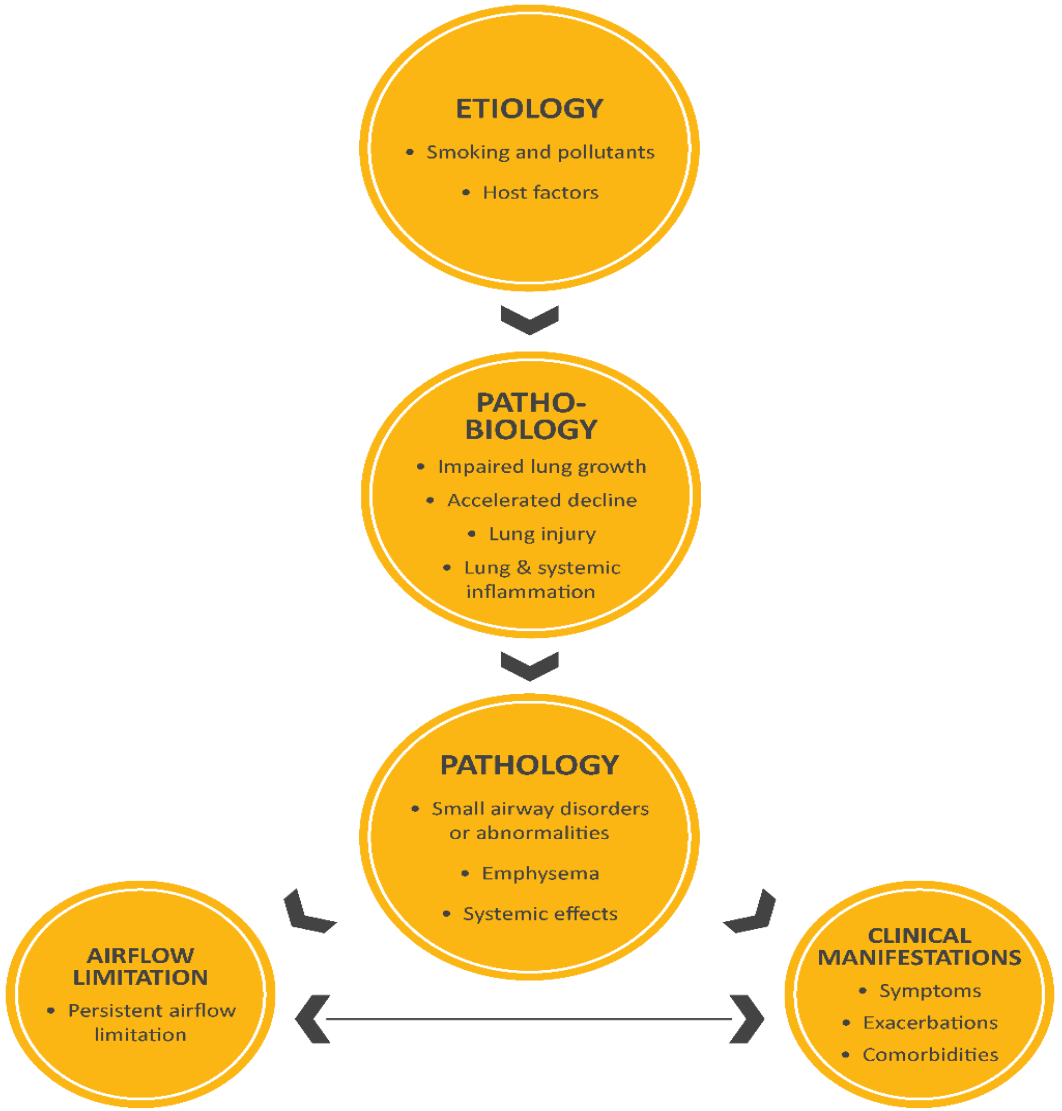


FIGURE 1.1

FEV_1 progression over time

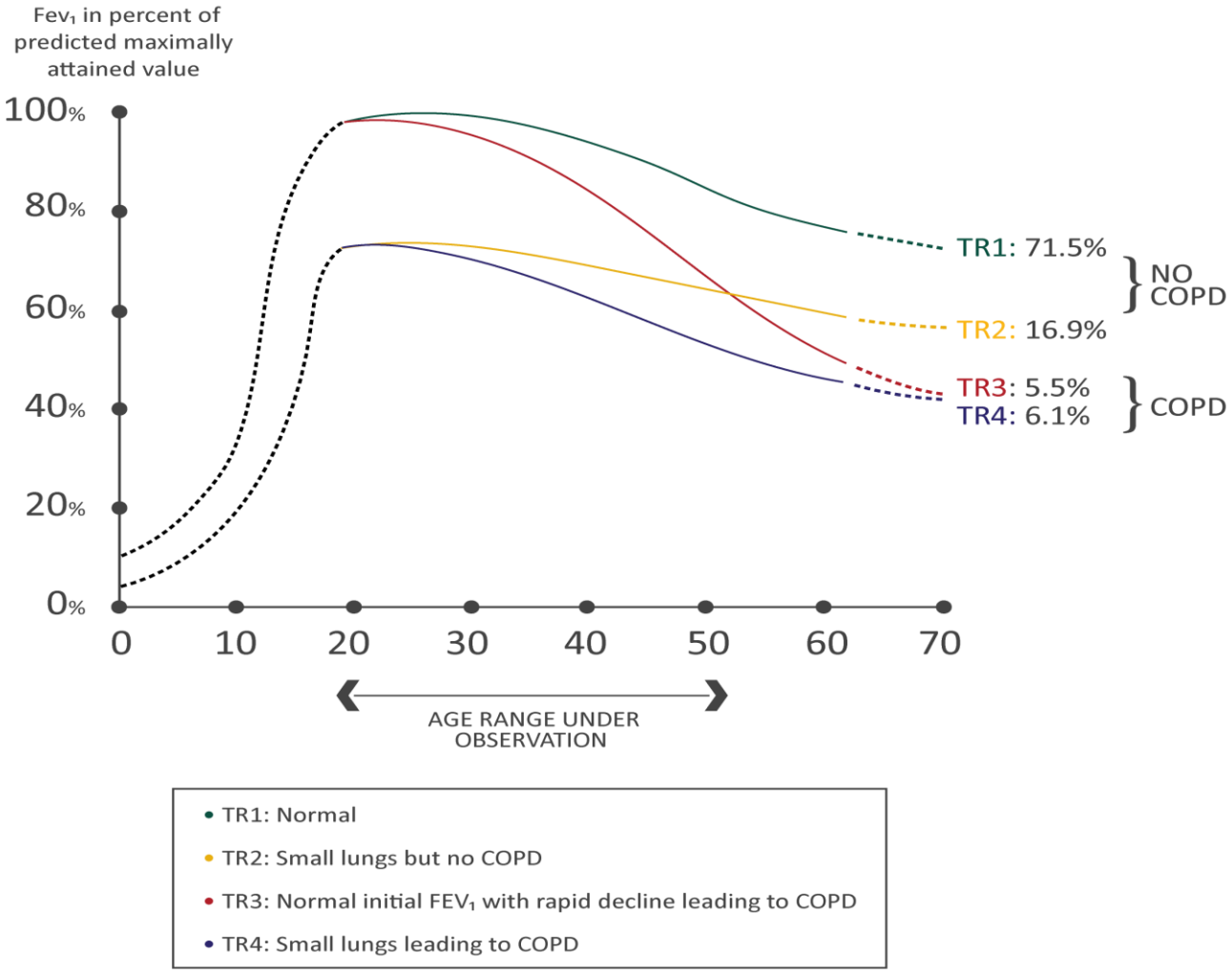


FIGURE 1.2

ABCD assessment tool

THE REFINED ABCD ASSESSMENT TOOL

Spirometrically Confirmed Diagnosis

Post-bronchodilator $FEV_1/FVC < 0.7$

Assessment of airflow limitation

Grade	FEV_1 (% predicted)
GOLD 1	≥ 80
GOLD 2	50-79
GOLD 3	30-49
GOLD 4	< 30

Assessment of symptoms/risk of exacerbations

Moderate or Severe Exacerbation History

≥2 or ≥ 1 leading to hospital admission

0 or 1 (not leading to hospital admission)

C	D
A	B

mMRC 0-1 CAT < 10 | mMRC ≥ 2 CAT ≥ 10

Symptoms

FIGURE 2.4

Treatment of stable COPD

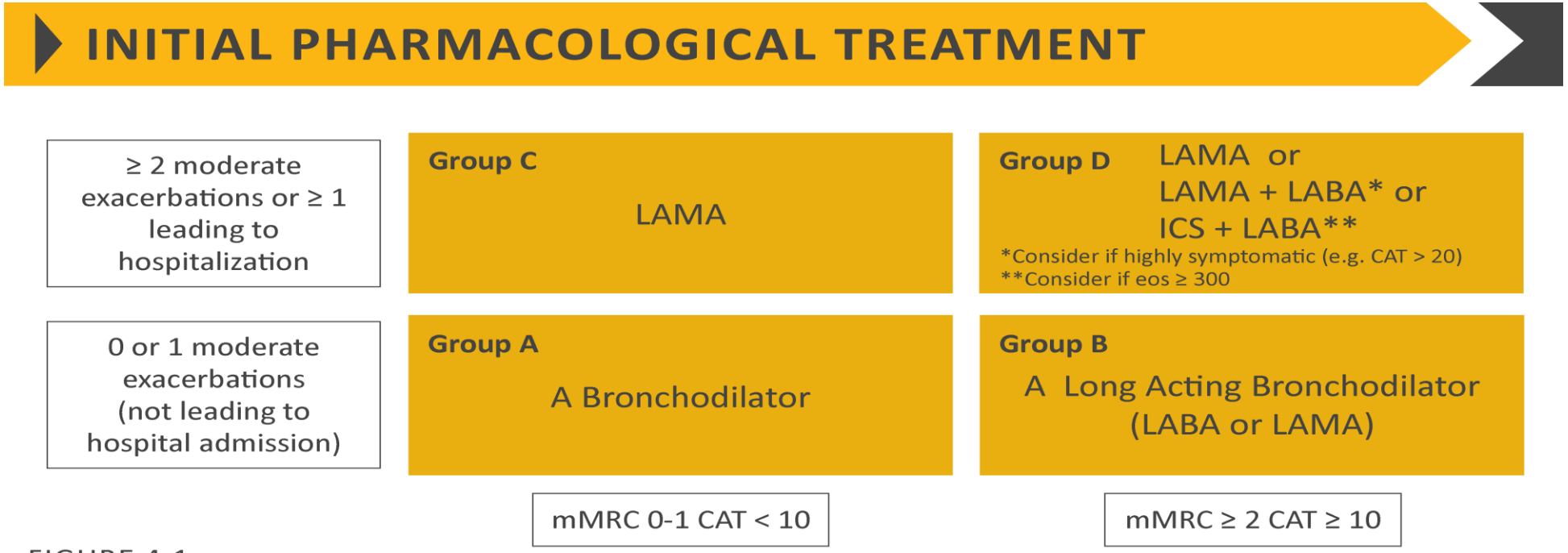
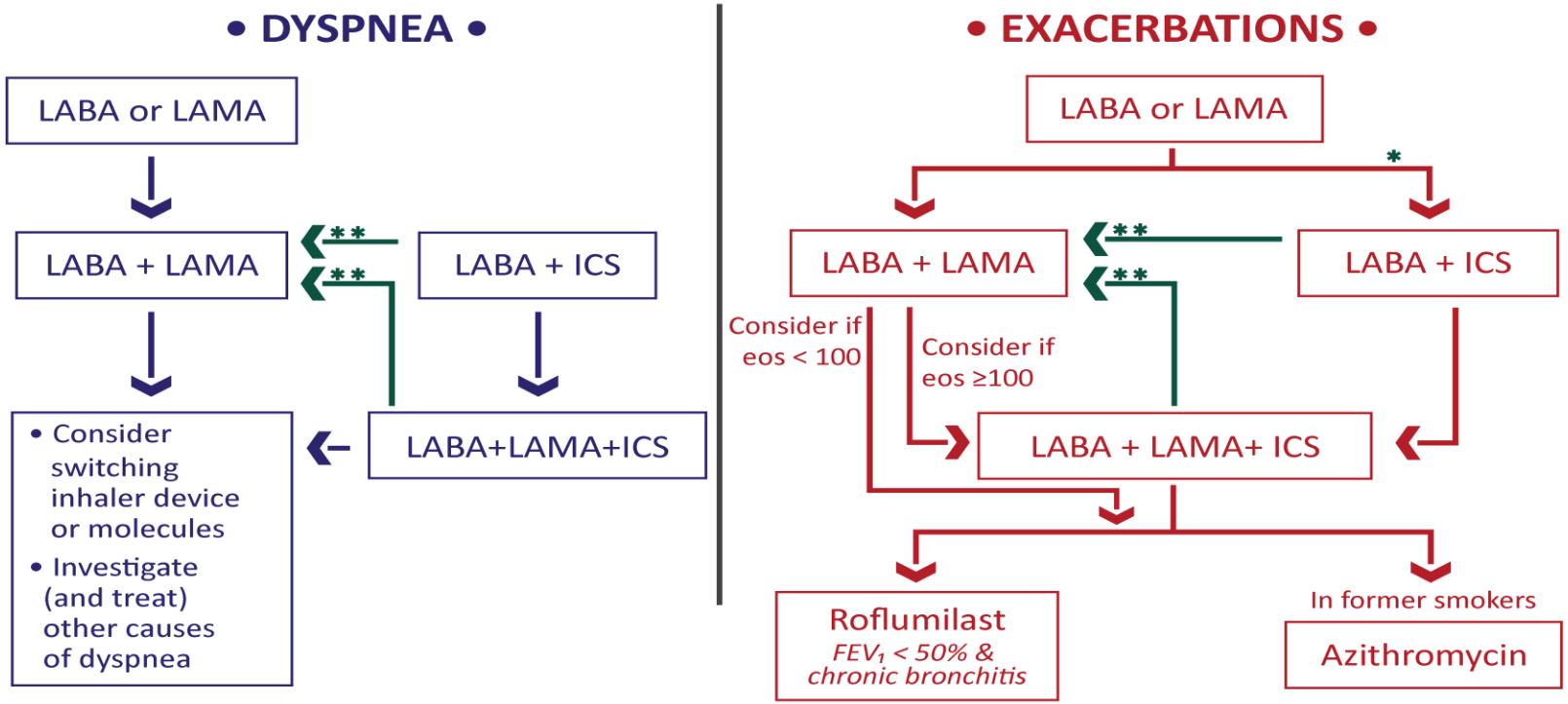


FIGURE 4.1

Definition of abbreviations: eos: blood eosinophil count in cells per microliter; mMRC: modified Medical Research Council dyspnea questionnaire; CAT™: COPD Assessment Test™.

FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. **IF NOT:**
   - ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - ✓ Place patient in box corresponding to current treatment & follow indications
   - ✓ Assess response, adjust and review
   - ✓ These recommendations do not depend on the ABCD assessment at diagnosis



eos = blood eosinophil count (cells/µL)
** Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization*
*** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*

FIGURE 4.3

Non-Pharmacological Treatment

- Education and self-management
- Physical activity
- Pulmonary rehabilitation programs
- Exercise training
- Self-management education
- End of life and palliative care
- Nutritional support
- Vaccination
- Oxygen therapy

Non-pharmacological treatment

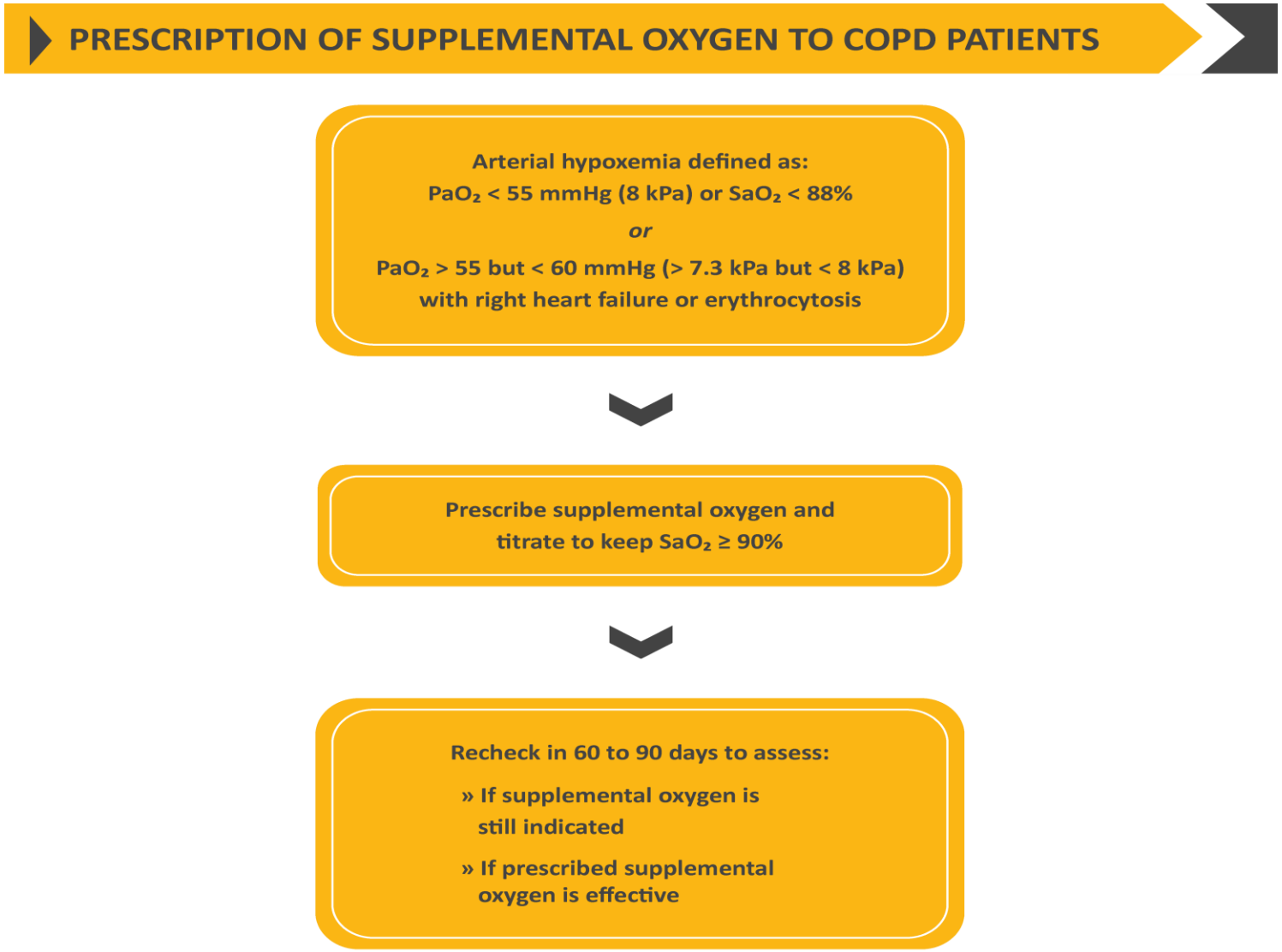


FIGURE 4.4

Non-pharmacological treatment

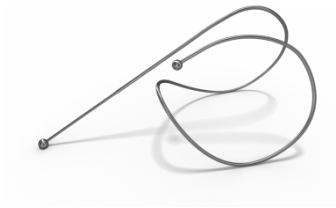
Interventional bronchoscopy & surgery

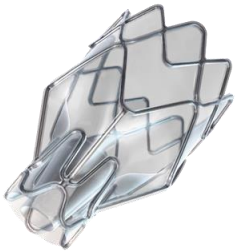
- In selected patients with heterogeneous or homogenous emphysema and significant hyperinflation refractory to optimized medical care, surgical or bronchoscopic modes of lung volume reduction (e.g., endobronchial one-way valves, lung coils or thermal ablation) may be considered.
- Some of these therapies (vapor ablation and lung coils) are not widely available for clinical care in many countries.
- In selected patients with a large bulla, surgical bullectomy may be considered.
- In selected patients with very severe COPD and without relevant contraindications, lung transplantation may be considered.

Techniques

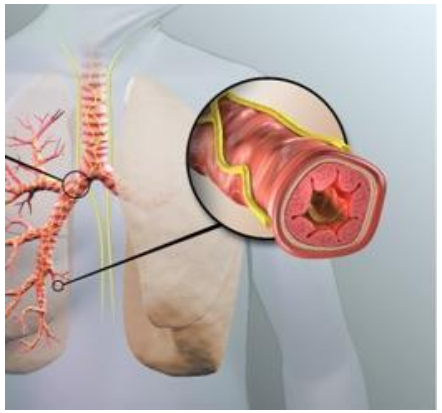
Plan

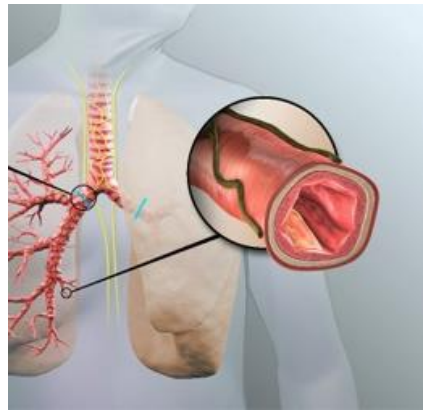
- Réduction d’emphysème
  - Pourquoi ?
  - Comment ?
  - Pour qui ?
  - Complications/survie



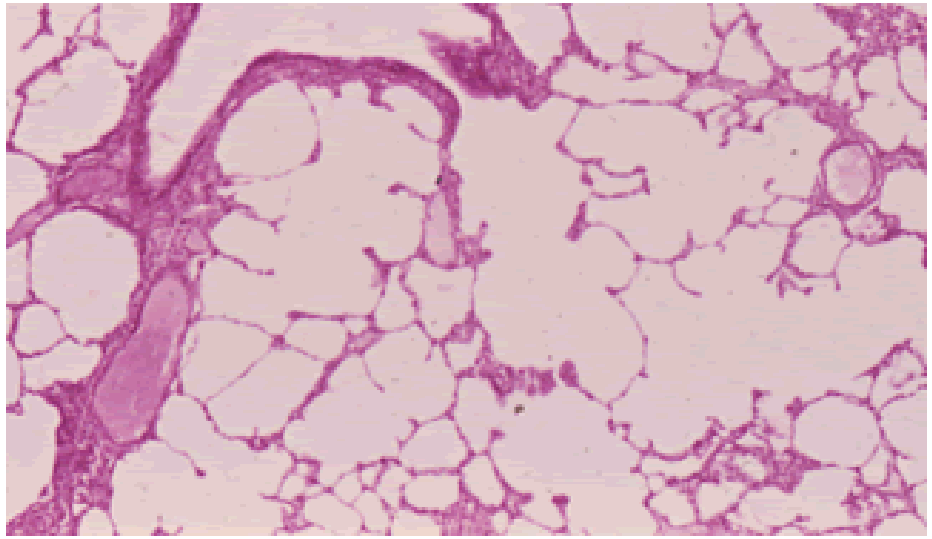


- Bronchodilatation permanente par dénervation
  - Concept ?
  - Protocole en cours





Réduction d’emphysème
Pourquoi ?



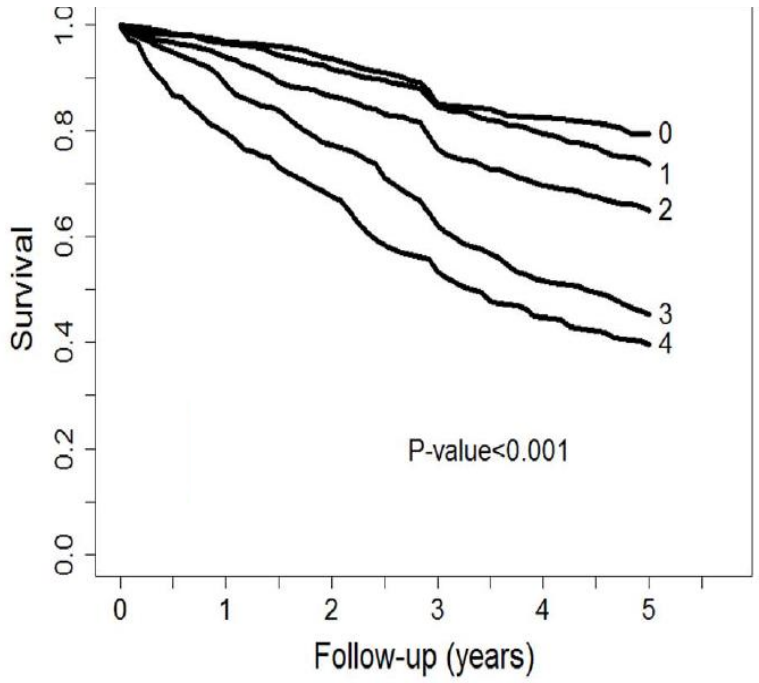
La BPCO, un problème grandissant de Santé Publique

- 250 000 morts par an en Europe (2)
- >10 milliards d'euros de dépenses directes en Europe (1)
- Dont 3 milliards d'euros par an en soins hospitaliers (1)
- 3ème cause de décès aux États-Unis et devrait être la 3ème cause mondiale d'ici 2030 (1)

Sources:
1) European COPD Coalition 2016
2) ERS The Burden of Lung Disease 2016

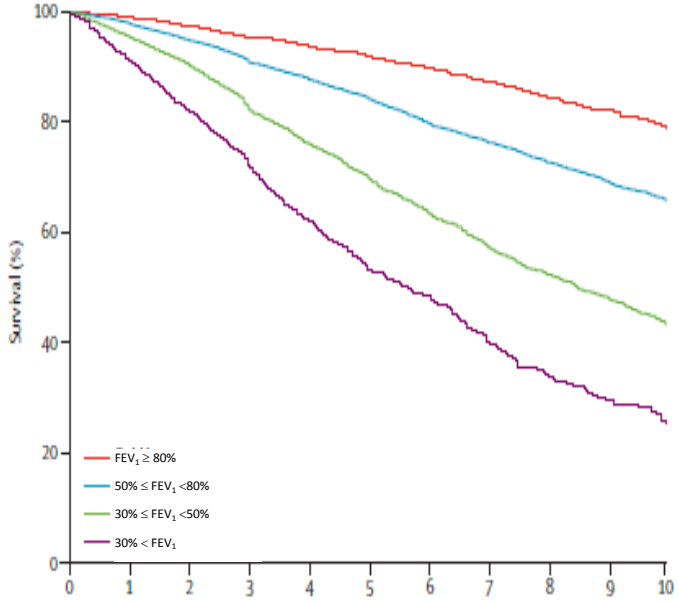
Patients à haut risque

Dyspnée
(mMRC)



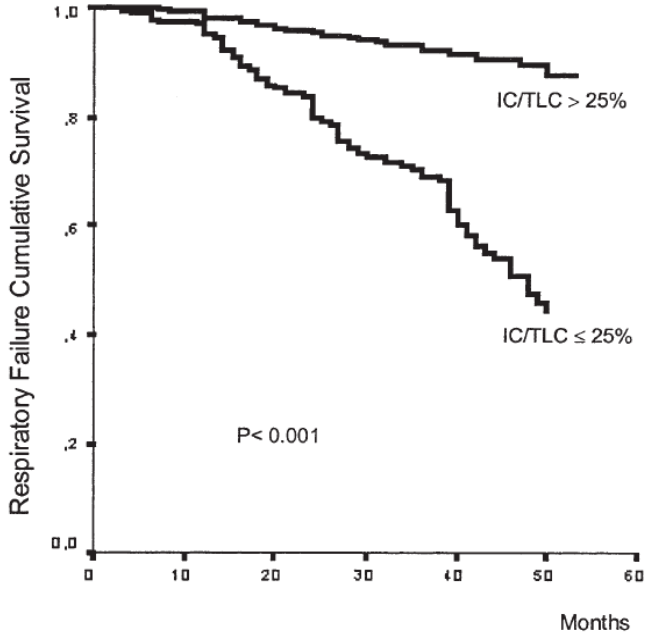
Almagro et al 2014 PlosOne
doi:10.1371/journal.pone.0089866

Obstruction
(VEMS)



Soriano et al 2015 Lancet Respir Med 2015; 3: 443–50

Hyperinflation

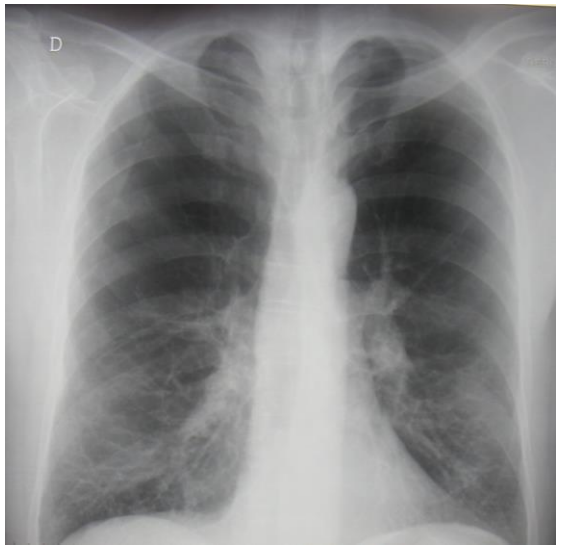


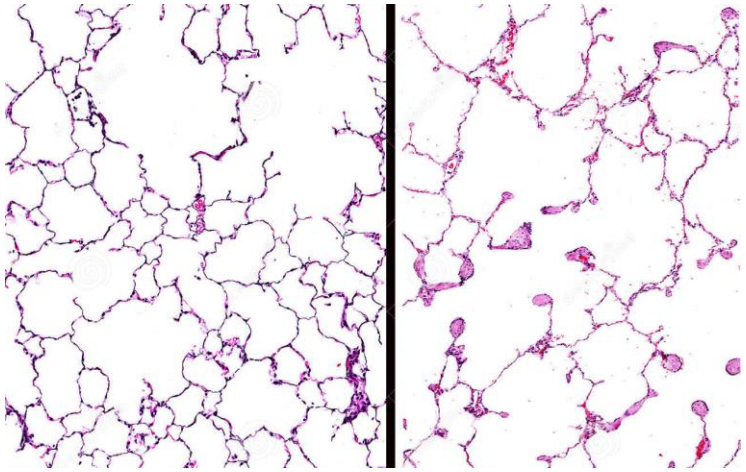
Casanova et al 2005 Am J Respir Crit Care Med Vol 171. pp 591–597

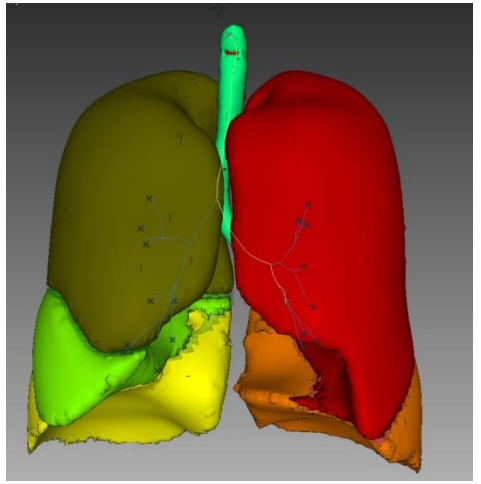
Pourquoi proposer une réduction de volume ?

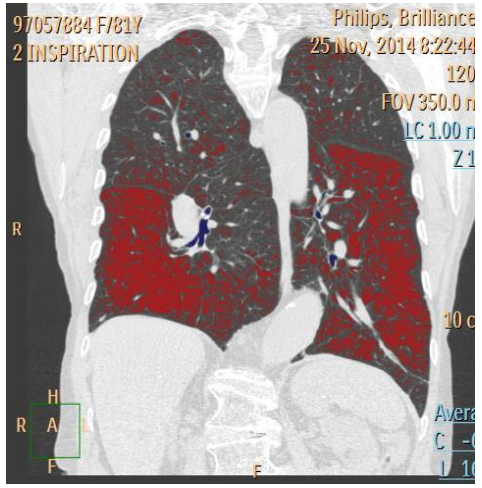
Améliorer les symptômes : Dyspnée d'effort

- Distension thoracique
- Hyperinflation (++ effort)
- Limitation débits ventilatoires
- Aplatissement diaphragme
- Compression structures saines adjacentes

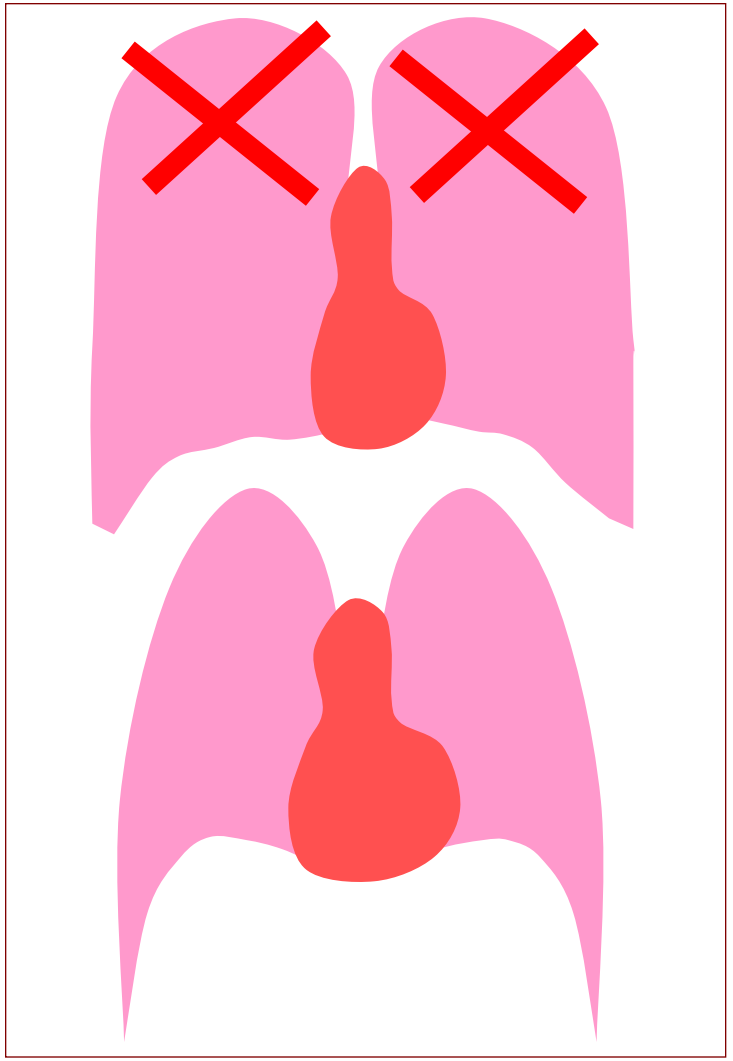






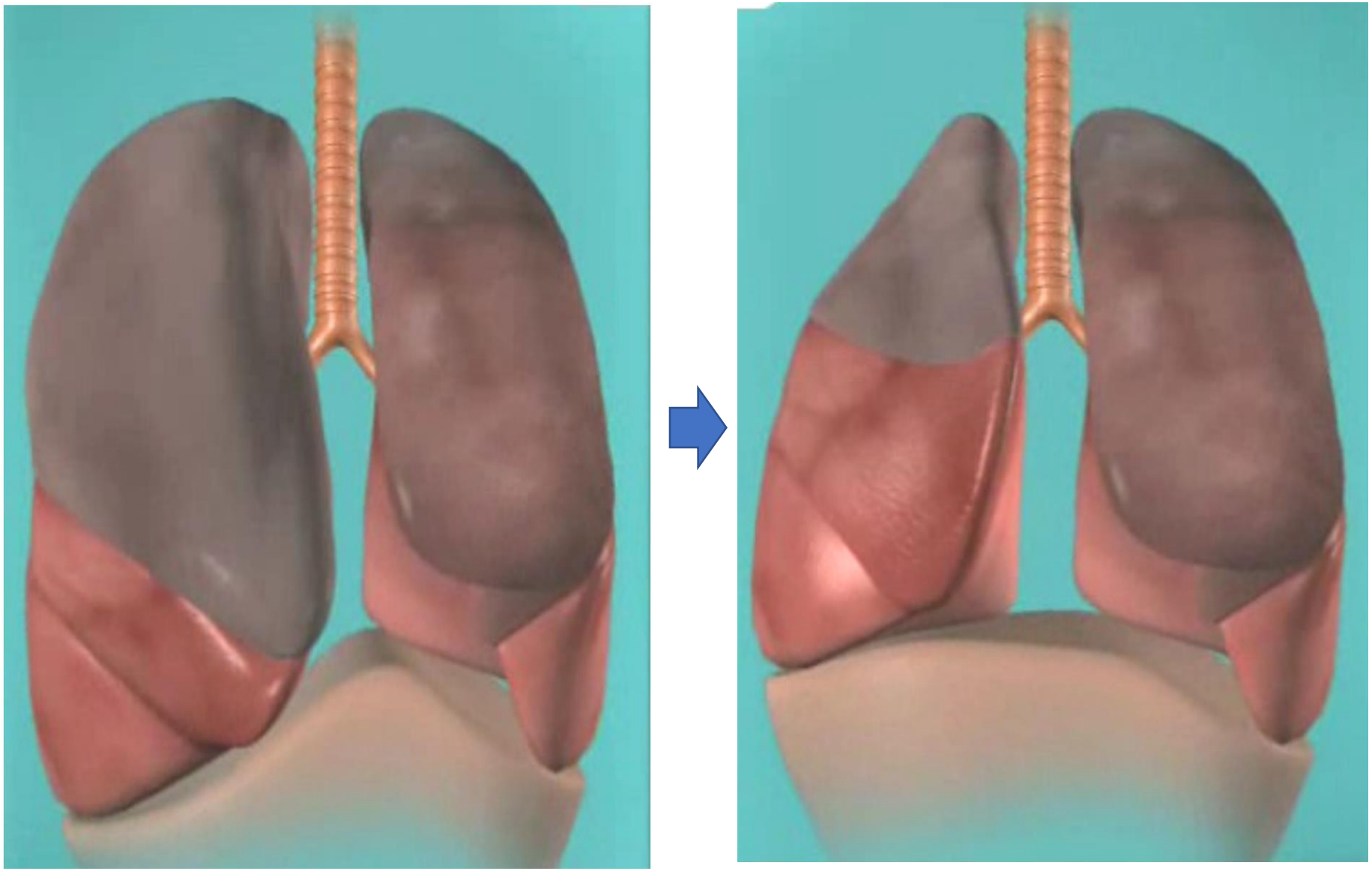


Une maladie qui prend de la place….



- Diminution de la distension thoracique (baisse du VR)
- Amélioration du rayon de courbure diaphragmatique (fonction musculaire inspiratoire)
- Amélioration des débits ventilatoires (augmentation CV et VEMS)

Amélioration dyspnée d'effort
Capacité à l'exercice
Qualité de vie

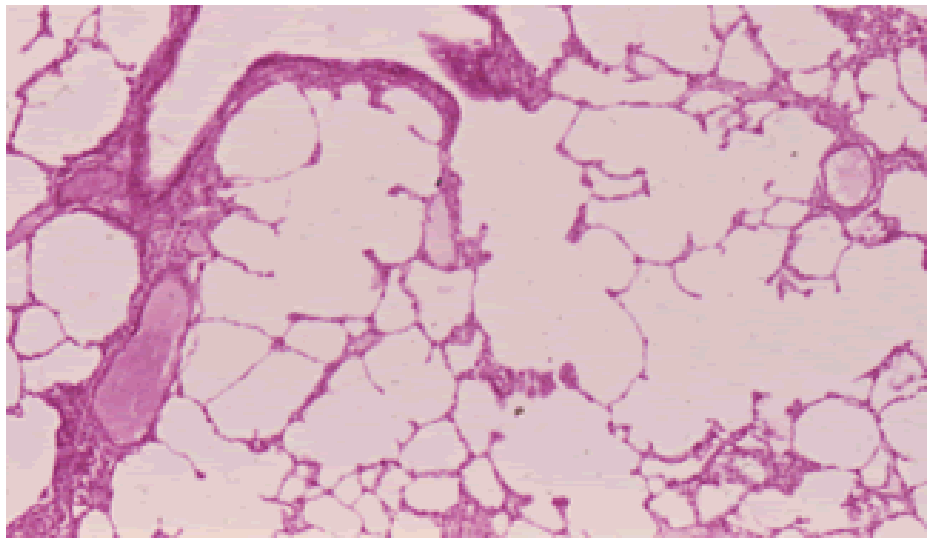


Recommandations GOLD 2019

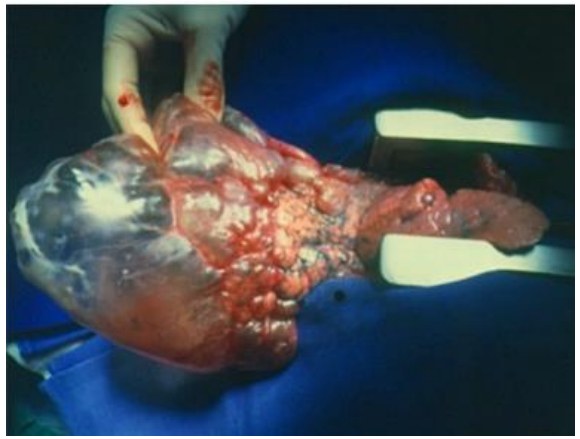
Table 3.11. Interventional therapy in stable COPD
Lung volume reduction surgery
• Lung volume reduction surgery improves survival in severe emphysema patients with an upper-lobe emphysema and low post-rehabilitation exercise capacity **(Evidence A)**.
Bullectomy
• In selected patients bullectomy is associated with decreased dyspnea, improved lung function and exercise tolerance **(Evidence C)**.
Transplantation
• In appropriately selected patients with very severe COPD, lung transplantation has been shown to improve quality of life and functional capacity **(Evidence C)**.
Bronchoscopic interventions
• In select patients with advanced emphysema, bronchoscopic interventions reduces end-expiratory lung volume and improves exercise tolerance, health status and lung function at 6-12 months following treatment. Endobronchial valves **(Evidence B)**; Lung coils **(Evidence B)**.

GOLD 2019 Report: GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Réduction d’emphysème
Comment ?



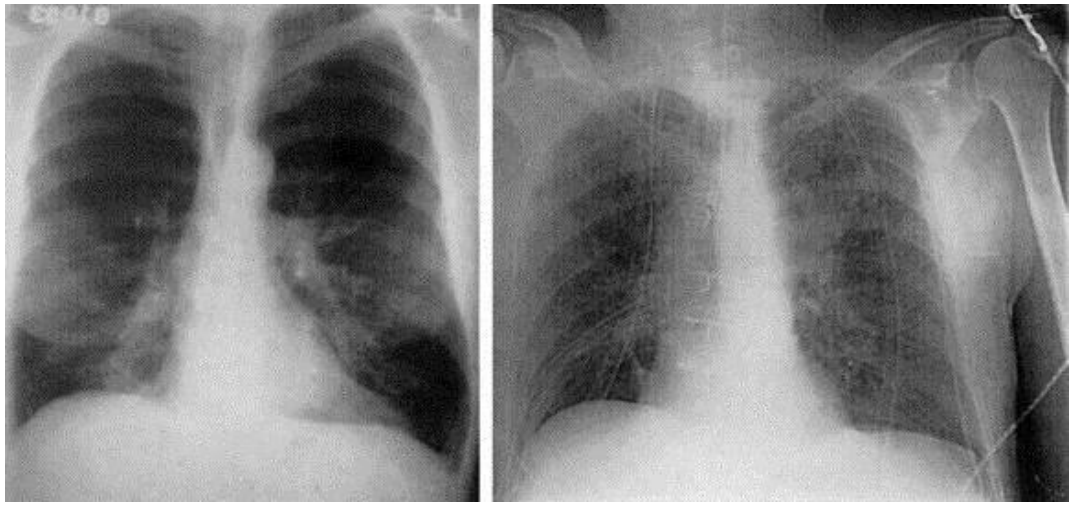
Réduction de volume chirurgicale



<u>1957</u> - Réduction de volume par double thoracotomie(1)

75 % des patients : amélioration clinique et fonctionnelle
MAIS 16 % de mortalité

<u>1990</u> - Résection bi-apicale par sternotomie médiane(2)



(2) Preoperative *(left)* and postoperative *(right)* x-ray film of 57-year old man. Endotracheal tube was removed immediately after chest x-ray film was taken. Film shows reconfiguration of chest and diaphragms. FEV_1 was 0.57 L before operation and 1.59 L at 3 months.

1. Brantigan OC, Mueller E. Surgical treatment of pulmonary emphysema. *Am Surg* 1957 ; 23 : 789-804.
2. Cooper JD *et al.* Bilateral pneumonectomy (volume reduction), for chronic obstructive pulmonary disease. *J Thorac Cardiovasc Surg* 1995 ; 109 : 106-16.

L'étude NETT en résumé

- Réduction de volume efficace sur la qualité de vie et la capacité à l'exercice

- **MAIS** importante morbi-mortalité
- Bénéfices que pour un petit groupe de patients, modérément atteints

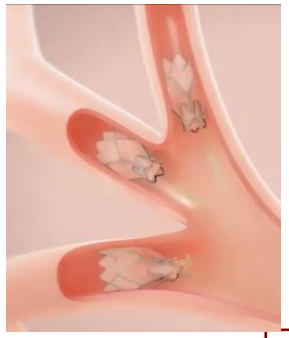
=> besoin de trouver d'autres solutions

Naunheim KS *et al.* Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial research group. *Ann Thorac Surg* 2006 ; 82 : 431-43.

Traitements par voie endobronchique dans l'emphysème

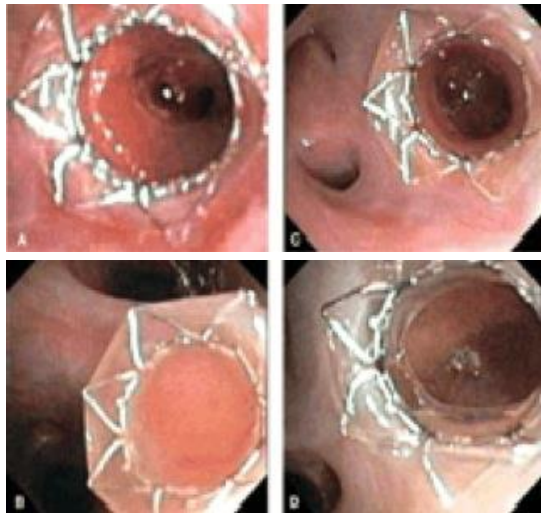
Modification de flux

Anatomique



Valves

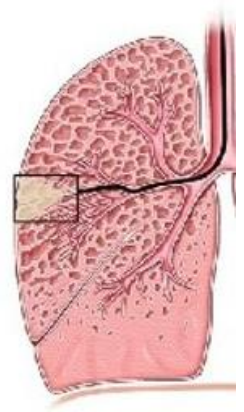
Extra-anatomique



Bypass

Effet mécanique loco-régional

Indirect

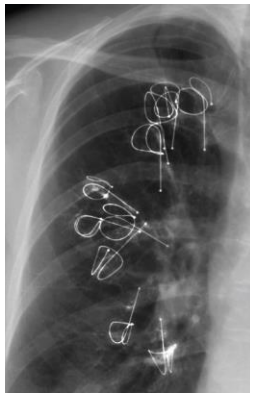


Colle biologique

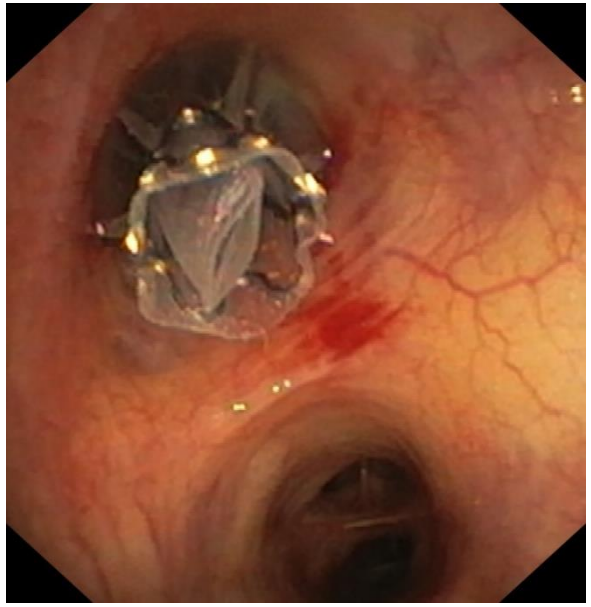
Vapeur thermique

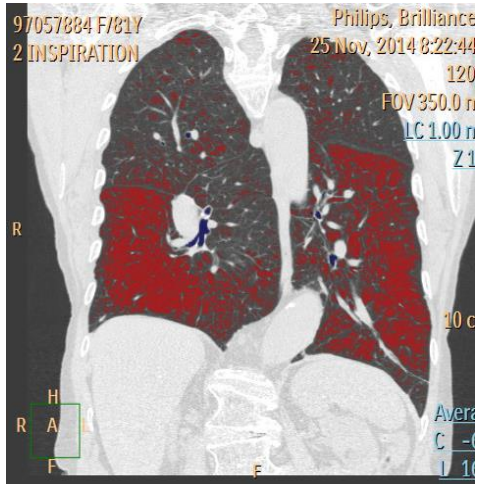
Direct

Spirales

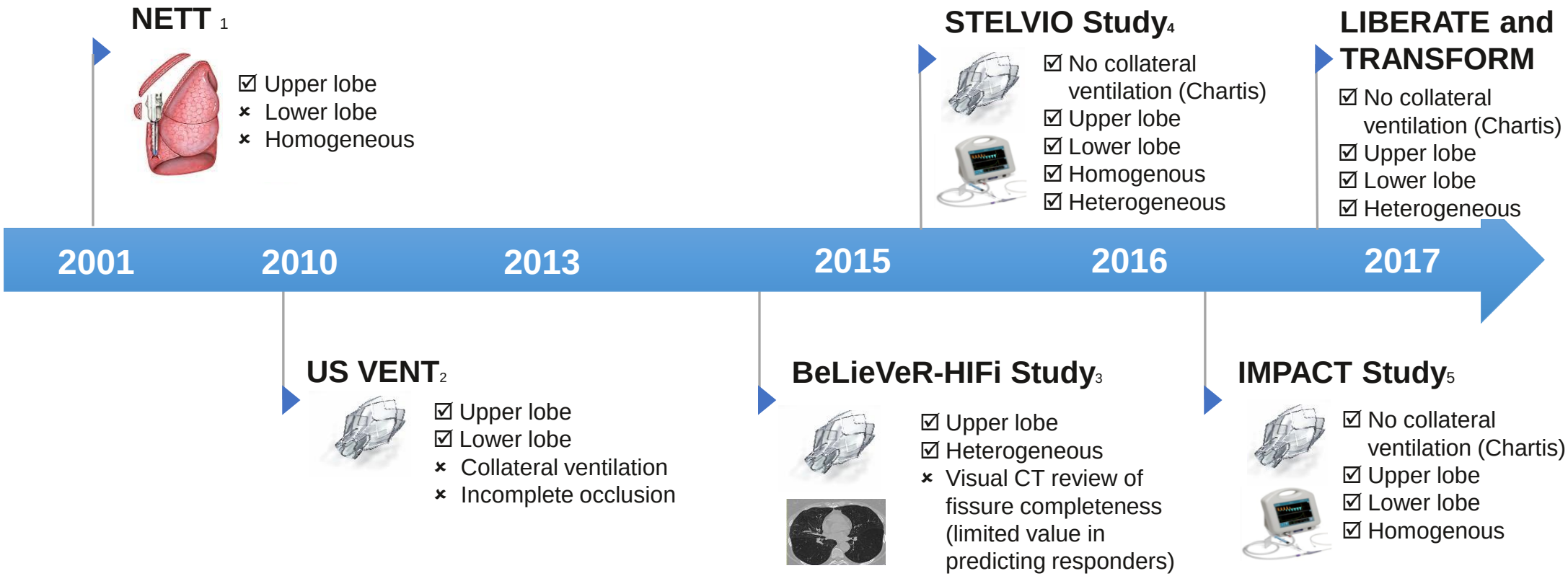


Valves anti-reflux ou uni-directionnelles



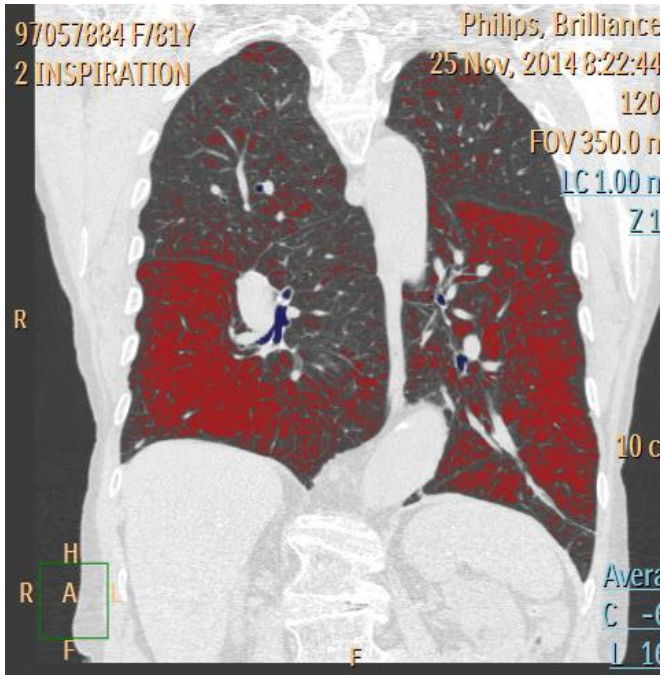


EndoBronchial Valve - EBV Reduction



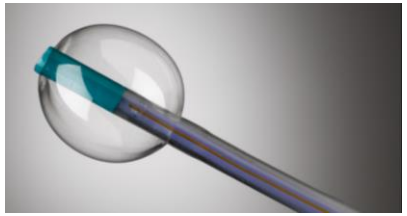
1. Fishman A et al. N Engl J Med 2003; 348: 2059-73.
2. Sciurba FC et al. N Eng J Med 2010; 363:1233-1244 (including supplementary appendix).
3. Davey C et al. Lancet 2015; 386: 1066-1073.
4. Klooster K et al. N Engl J Med 2015; 373(24): 2325-2335.
6. Valipour A et al, AJRCCM 2016. 194: 1073–1082

Réduction d'emphysème par valves unidirectionnelles



choix du lobe :

- Scanner et StratX®
- Scintigraphie ventilation/perfusion
- réalisation d'une fibroscopie
- mesure des ventilations collatérales avec le dispositif CHARTIS®



Slebos DJ. Endobronchial Valves for Endoscopic Lung Volume Reduction: Best Practice Recommendations from Expert Panel on Endoscopic Lung Volume Reduction. Respiration. 2017;93(2):138-150.

Quelle évaluation pré-EBV ?

StratX@

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	97.9	98.9	94.0	98.9	100.0	100.0
% Voxel Density Less Than -910 HU	85	84	62	59	81	60
% Voxel Density Less Than -950 HU	71	70	41	34	63	32
Inspiratory Volume (ml)	1765	1824	59	1793	1601	1995

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	69.5	91.6	74.5	91.6	96.2	96.2
% Voxel Density Less Than -910 HU	71	69	54	44	57	33
% Voxel Density Less Than -950 HU	54	52	35	28	39	19
Inspiratory Volume (ml)	1903	2157	254	1202	1801	916

Réduction d'emphysème par valves unidirectionnelles

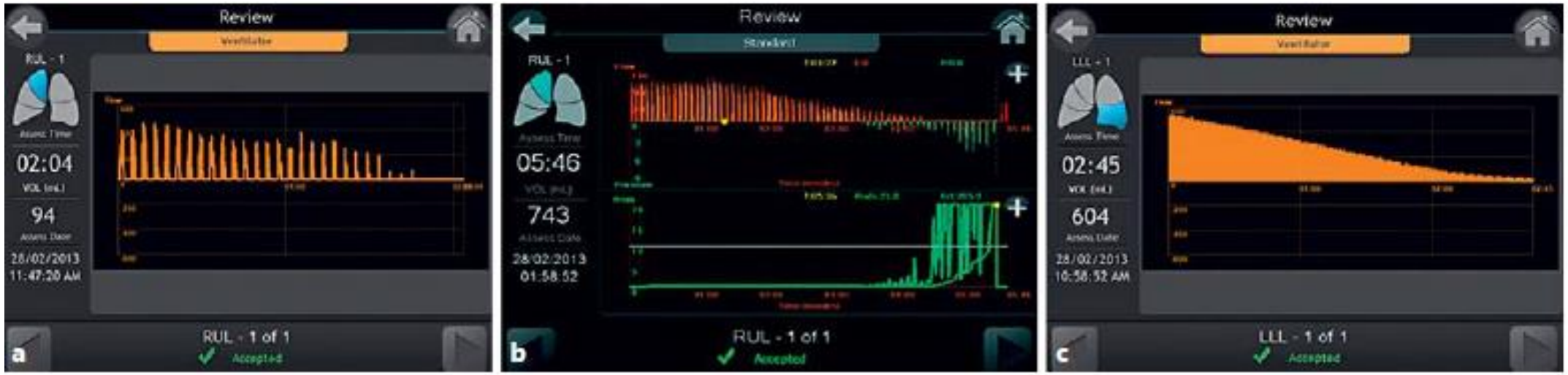
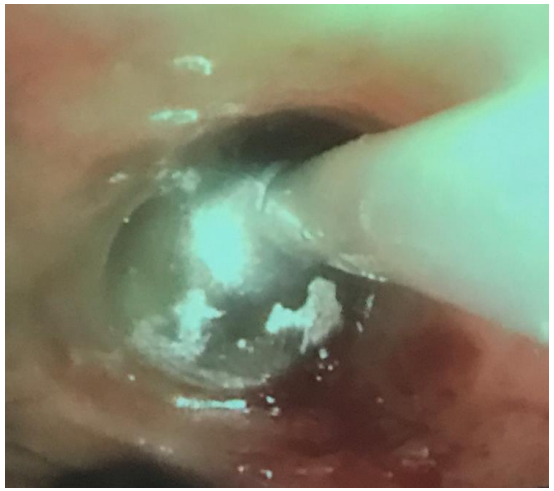
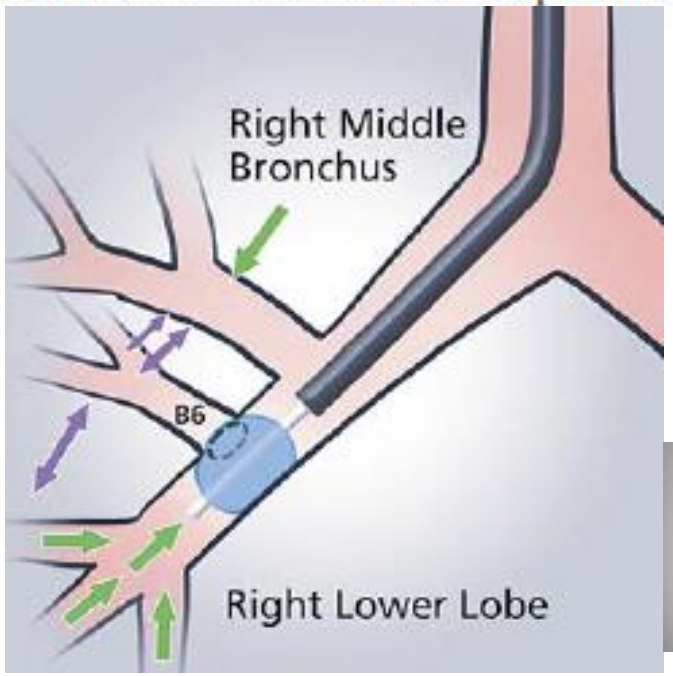
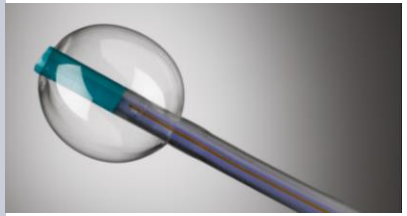


Fig. 6. Chartis procedure showing absence of collateral flow performed under different anesthetic methods. **a** Positive pressure ventilation. **b** Conscious sedation. **c** Jet ventilation.

Si scissures complètes entre 80-95%

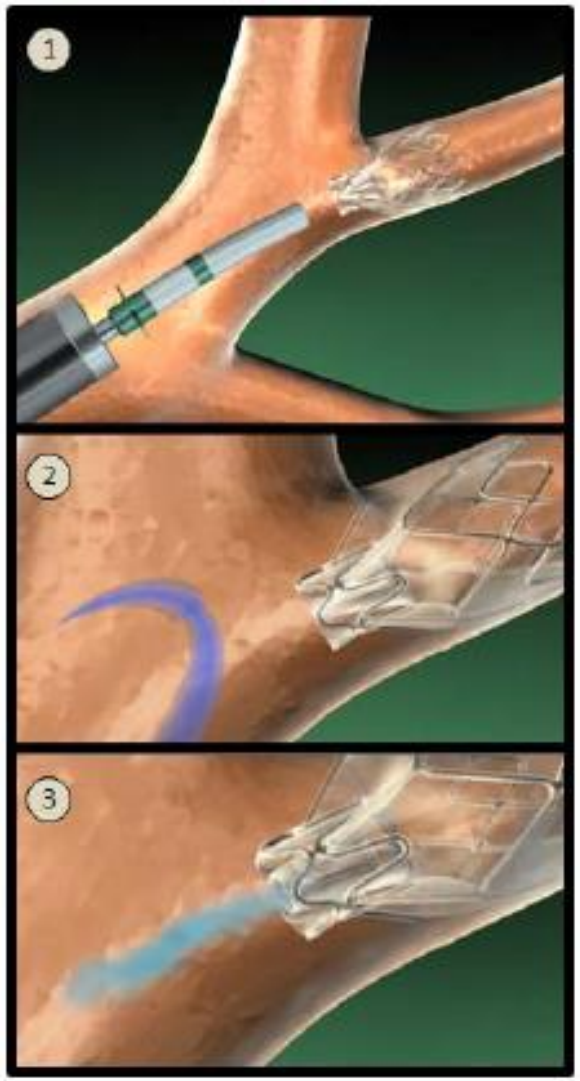






Slebos DJ. Endobronchial Valves for Endoscopic Lung Volume Reduction: Best Practice Recommendations from Expert Panel on Endoscopic Lung Volume Reduction. Respiration. 2017;93(2):138-150.

si pas de VC, pose d'une ou plusieurs valves par endoscopie :

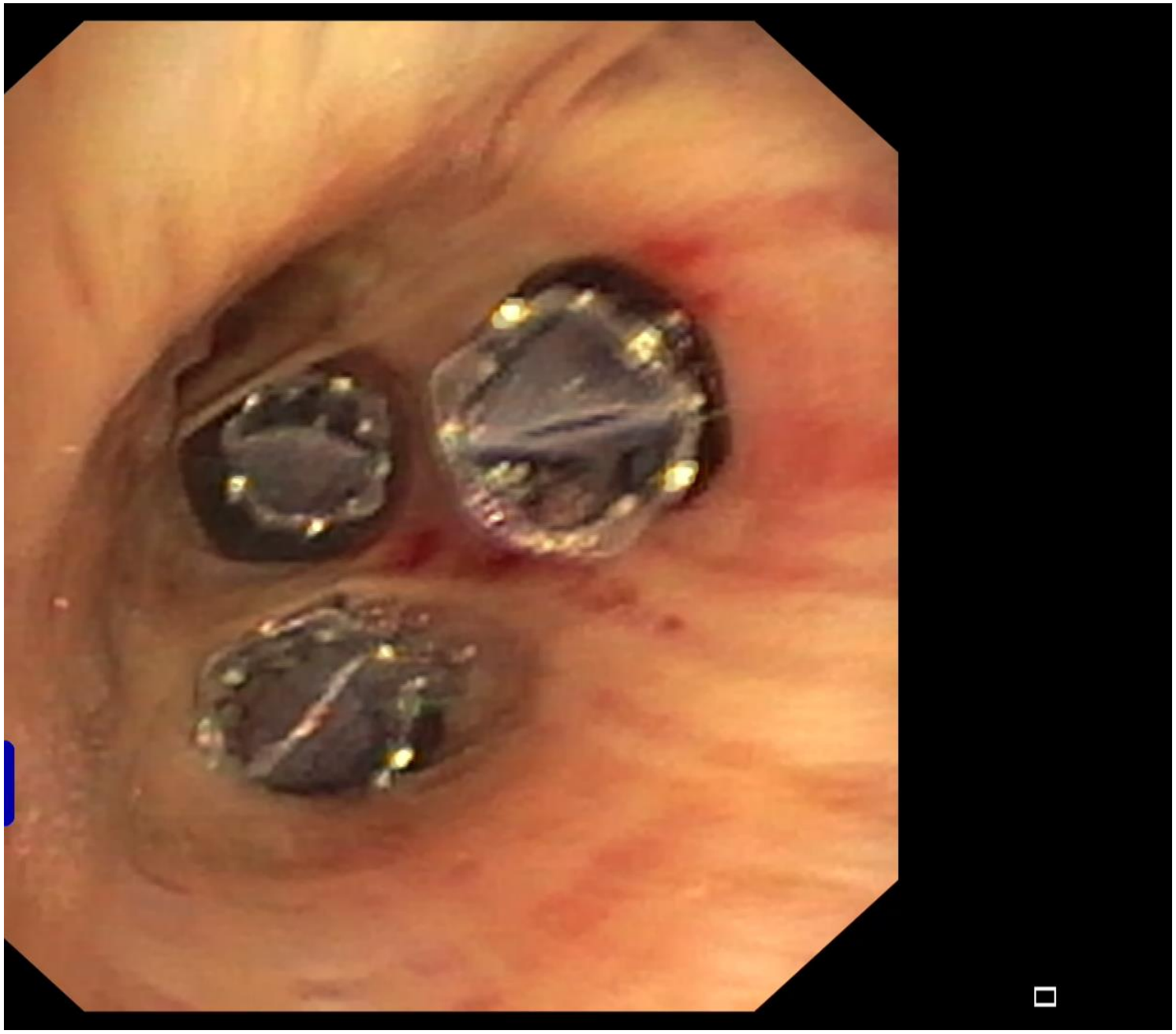


• mise en place de la valve à l'aide d'un cathéter

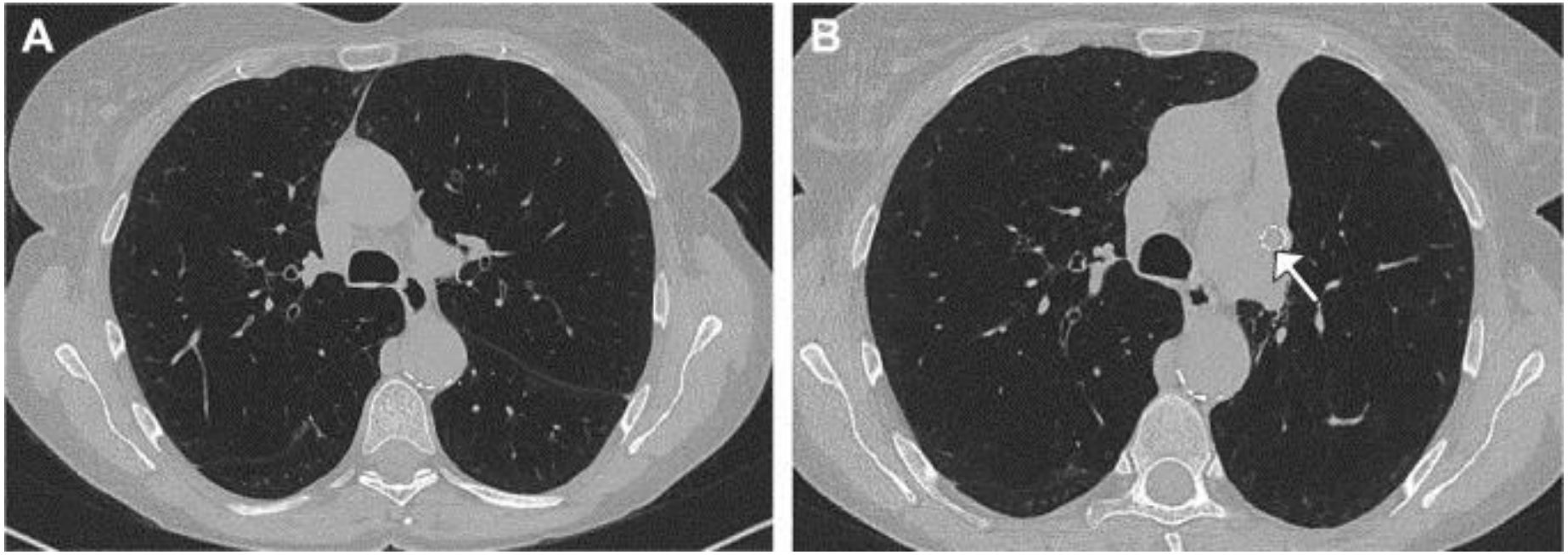
• la valve se ferme à l'inspiration

•La valve s'ouvre à l'expiration

Etude VENT : A randomized study of endobronchial valves for advanced emphysema. Sciurba FC, Ernst A, Herth FJ, Strange C, Criner GJ, Marquette CH, Kovitz KL, Chiacchierini RP, Goldin J, McLennan G, VENT Study Research Group, N Engl J Med. 2010;363(13):1233



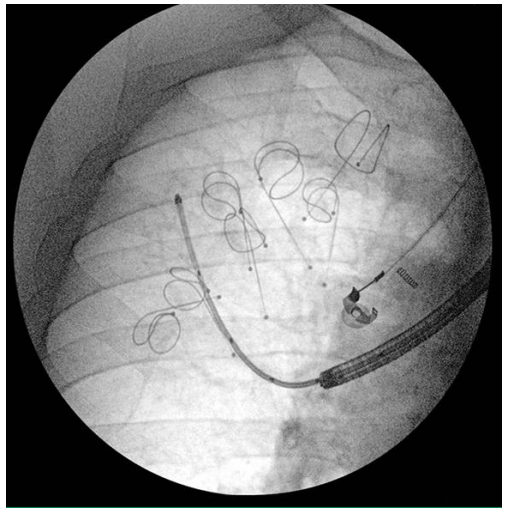
Atélectasie complète du LSG après pose de valve

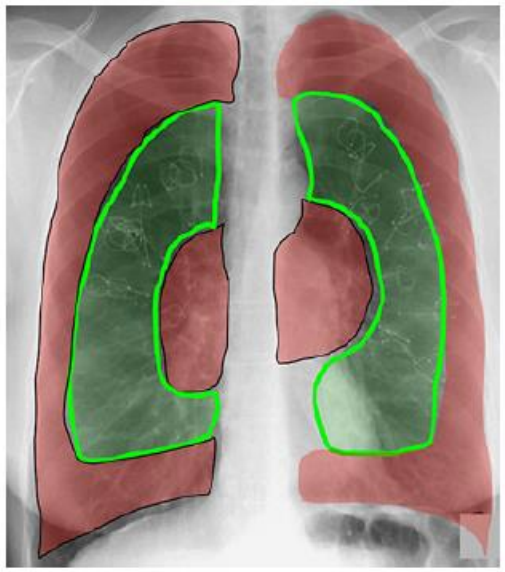


Endoscopic bronchial valve treatment: patient selection and special considerations.
Eberhardt R, Gompelmann D, Herth FJ, Schuhmann M. Int J Chron Obstruct Pulmon Dis. 2015 Oct 8;10:2147-57.

Traitement par spirales

La technique…



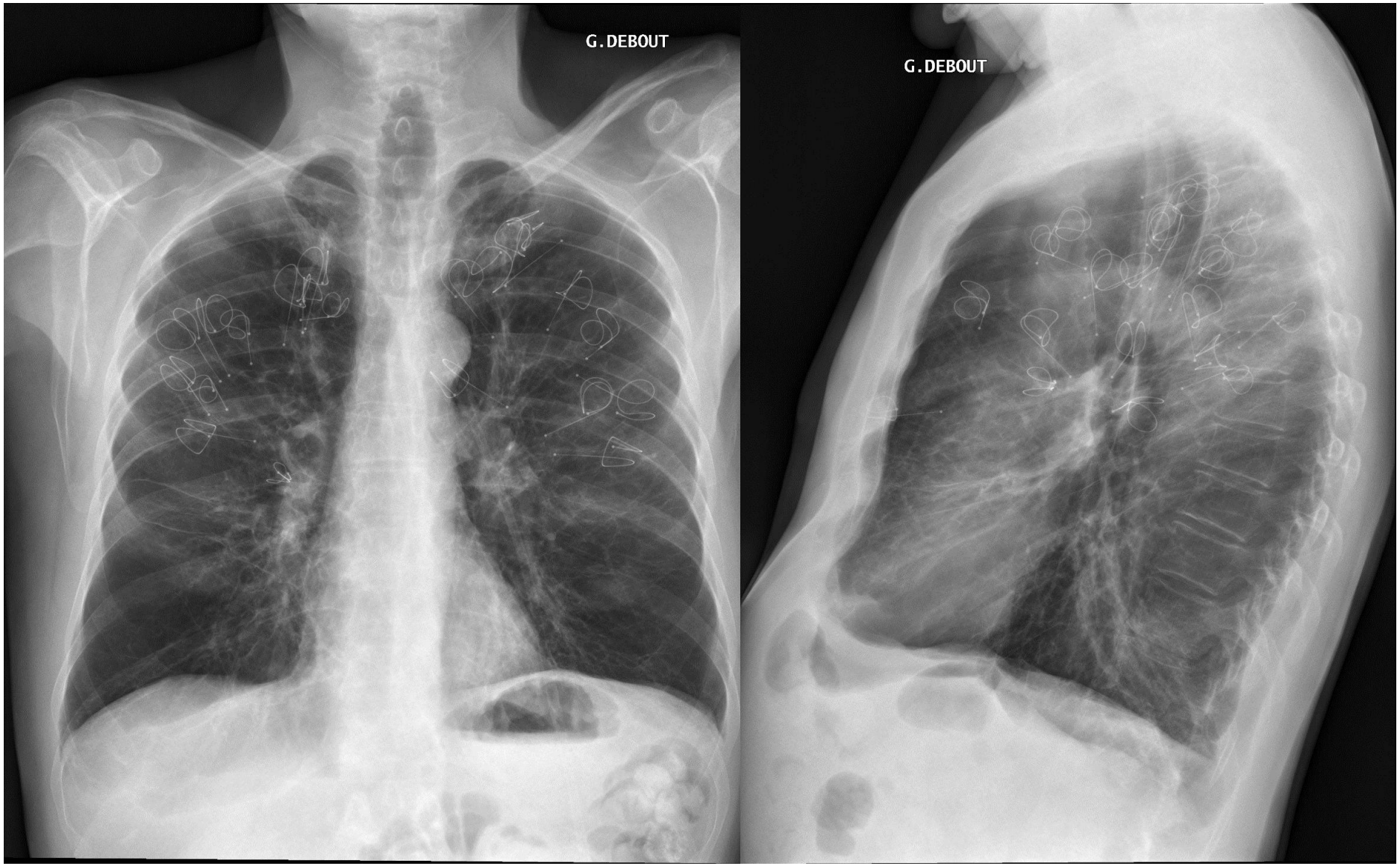


- Anesthésie générale
- Intubation trachéale (8-9)
  (masque laryngé possible)

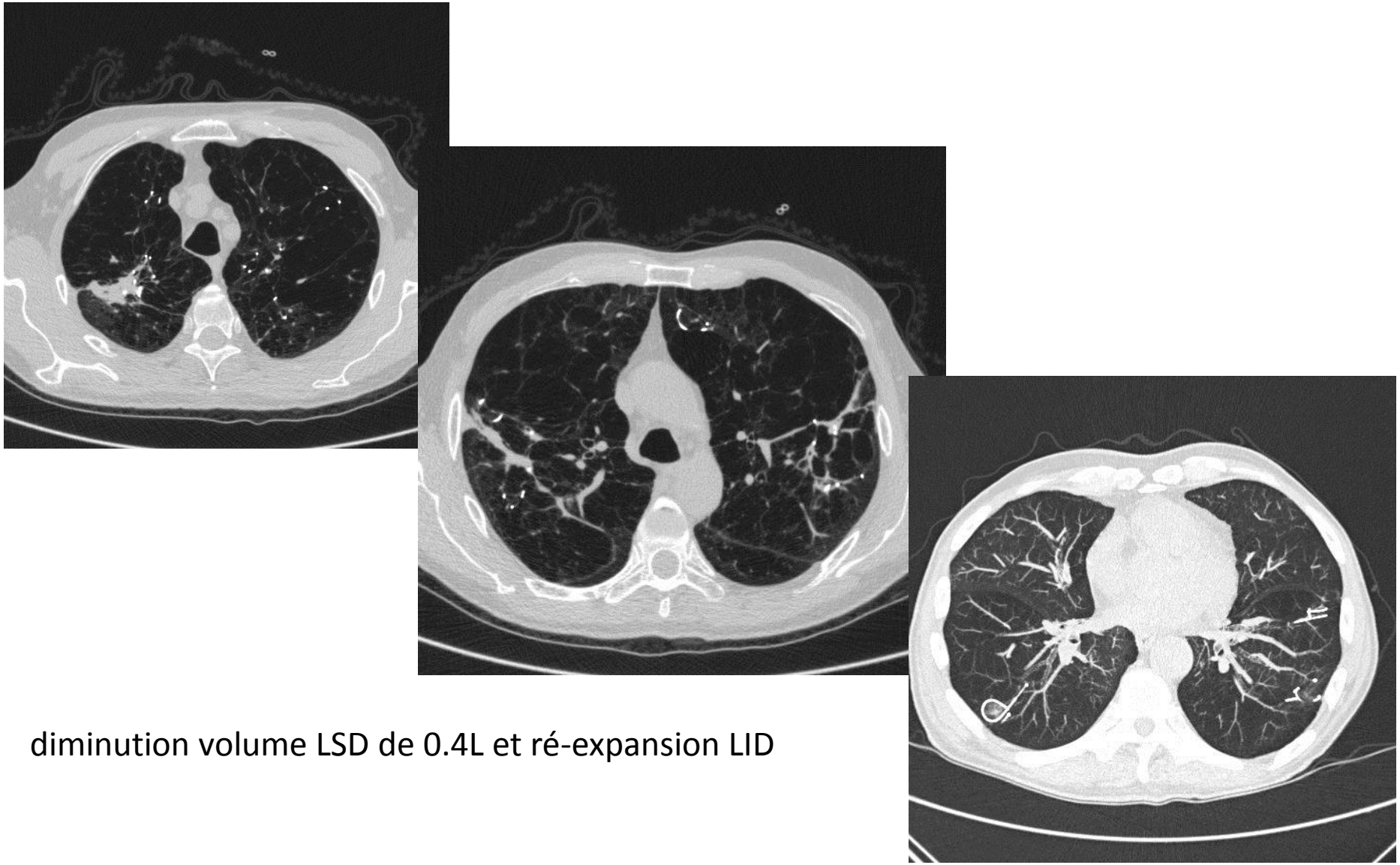
- Bronchoscopie souple (2.8 mm)
- Radioscopie

- 1 lobe par procédure
- 8 à10 coils par lobe
- Traitement bilatéral en 2 procédures
  séquentielles (>1 mois)

2 procédures pour traiter 2 lobes de manière bilatérale

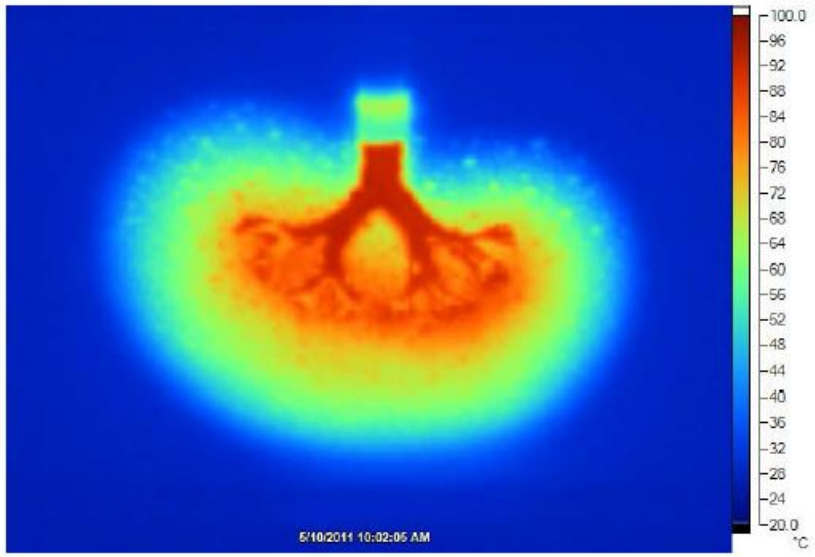


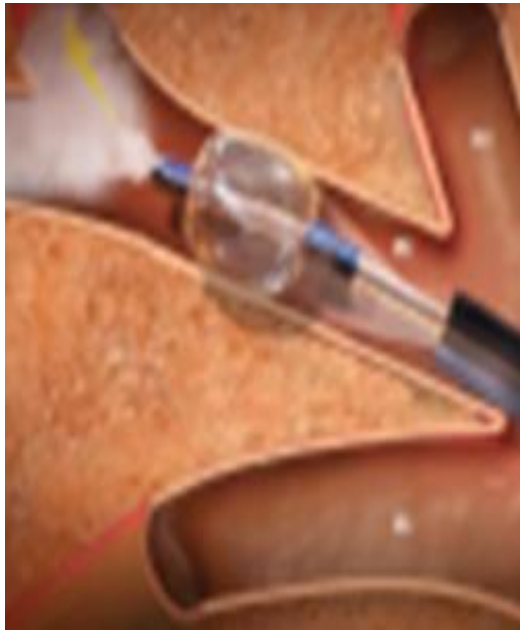
Scanner à 6 mois



diminution volume LSD de 0.4L et ré-expansion LID

Vapeur endobronchique





Réduction d'emphysème par vapeur endobronchique

- Inventée en 2005 aux USA
- Créer une réduction sans dispositifs implantables
- Efficace sur CV + ou CV -

"the garage"

Robert Barry
Chief Clinical & Research Officer
Founder & Inventor
Uptake Medical Technology
Seattle, WA USA

Lung Volume Reduction (LVR) - shrinkage

Swine upper lobe
(pre-vapor treatment)

Swine upper lobe
(post-vapor treatment)

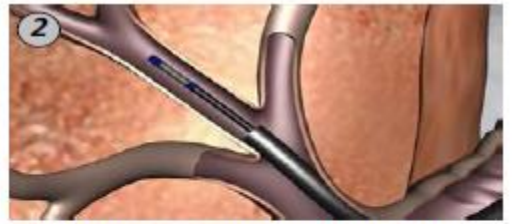
Swine upper lobe
Cross- section
(post-vapor treatment)

Réduction d'emphysème par vapeur endobronchique

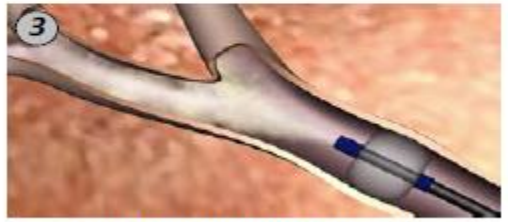
HRCT

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

- Lobe déterminé par scanner
- Traitement : 5 cal/g de masse des segments cibles
- Vapeur délivrée par bronchoscopie entre 3-10 secondes
- Occlusion par un ballonnet

Réduction d’emphysème
Pour qui ?

Sélection des patients pour réduction par valves

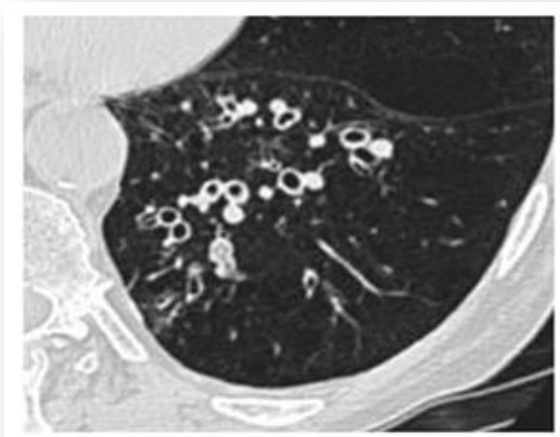
- **Volume Résiduel > 175%, CPT > 100%**
- **VEMS entre 15% et 50%, DLCO > 20%**
- **Absence de ventilation collatérale dans le lobe cible avec lobes adjacents**
- **Emphysème > 50%, préférence hétérogène, scissures 80-95% ou > 95% (CI° <80%)**

- Etat clinique stable (pas EABPCO > 6 semaines),< 3 exacerbations dans les 12 derniers mois
- Pas d'autres pathologies pulmonaires que l'emphysème sur TDM
- Anesthésie et bronchoscopie possible
- Sevrage tabagique (> 8 semaines), réhabilitation faite, ttt médical et paramédical optimal

Contre-indications

- Sévérité :
  - PaO2 < 45 mmHg aa et/ou PaCO2 > 60mmHg (possible si amélioration après 3 mois VNI)
  - PM6 < 200m (possible réévaluation après réhabilitation), indication 100-500m
  - Exacerbateur et sécrétant, colonisation à pyo ou SAMR
  - Bulles > 1/3 du poumon
- Pathologie cardiovasculaire instable
- ATCD de chirurgie thoracique :
  - Même côté : chirurgie ou pleurodèse (adhérences, défaut de compliance)
  - Controlatéral : pas de CI si ATCD bullectomie, résection lobaire, segmentaire ou wedge
- aAT et HTAP pas de contre-indication mais manque d'études

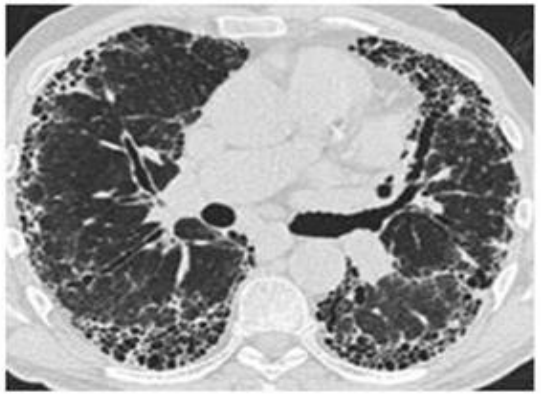
Contre-indications



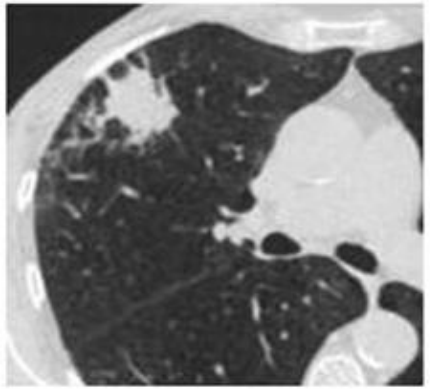
Airway disease

Bronchiectasis

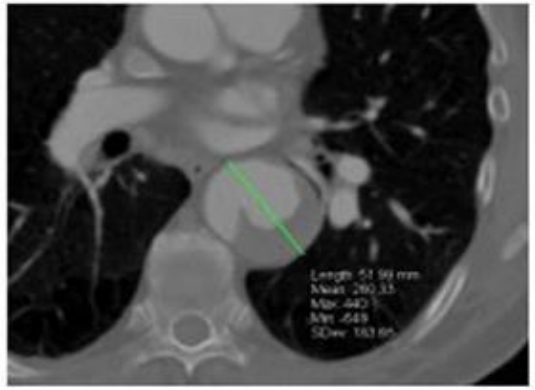
Paraseptal Emphysema



Fibrosis

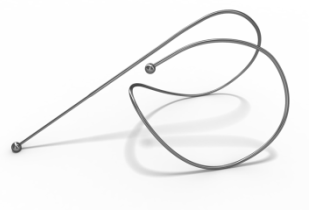


Suspicious nodule



Accidental findings

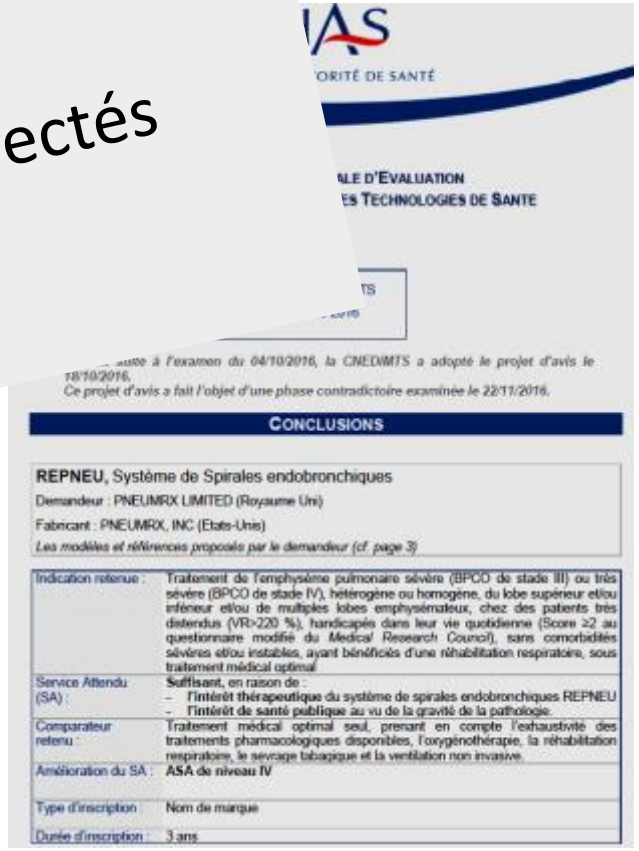
Qui sont les candidats potentiels aux coils ?



- La CNEDIMTS retient l'indication suivante:
  - Traitement de l'**emphy**
    - sévère o
    - hétérogè
    - des lobes
  - Chez des **pati**
    - très distend
    - handicapés d
    - Non exacerba
    - sans comorbid
    - sous traitement médical optimal
    - ayant bénéficié d'une réhabilitation respiratoire
    - Sevré du tabac

Contre-indications :

- Atteinte cardio-vasculaire
- Atteinte bronchique
- Exacerbateurs fréquents, colonisés ou infectés
- Autres pathologies pulmonaires
- ….. ou instables



…ORITÉ DE SANTÉ

…LE D'EVALUATION
…ES TECHNOLOGIES DE SANTE

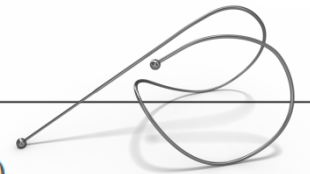
…ute à l'examen du 04/10/2016, la CNEDIMTS a adopté le projet d'avis le 18/10/2016.
Ce projet d'avis a fait l'objet d'une phase contradictoire examinée le 22/11/2016.

CONCLUSIONS

REPNEU, Système de Spirales endobronchiques
Demandeur : PNEUMRX LIMITED (Royaume Uni)
Fabricant : PNEUMRX, INC (Etats-Unis)
Les modèles et références proposés par le demandeur (cf. page 3)

Indication retenue :	Traitement de l'emphysème pulmonaire sévère (BPCO de stade III) ou très sévère (BPCO de stade IV), hétérogène ou homogène, du lobe supérieur et/ou inférieur et/ou de multiples lobes emphysémateux, chez des patients très distendus (VR>220 %), handicapés dans leur vie quotidienne (Score ≥2 au questionnaire modifié du Medical Research Council), sans comorbidités sévères et/ou instables, ayant bénéficiés d'une réhabilitation respiratoire, sous traitement médical optimal
Service Attendu (SA) :	**Suffisant**, en raison de : – **l'intérêt thérapeutique** du système de spirales endobronchiques REPNEU – **l'intérêt de santé publique** au vu de la gravité de la pathologie.
Comparateur retenu :	Traitement médical optimal seul, prenant en compte l'exhaustivité des traitements pharmacologiques disponibles, l'oxygénothérapie, la réhabilitation respiratoire, le sevrage tabagique et la ventilation non invasive.
Amélioration du SA :	**ASA de niveau IV**
Type d'inscription :	Nom de marque
Durée d'inscription :	3 ans

Qui sont les candidats potentiels aux coils ?



Respiration

Thematic Review Series

Respiration
DOI: 10.1159/000490193

Published online: July 10, 2018

Endobronchial Coils for Endoscopic Lung Volume Reduction: Best Practice Recommendations from an Expert Panel

Dirk-Jan Slebos[a, b] Nick H. ten Hacken[a, b] Martin Hetzel[c] Felix J.F. Herth[d]
Pallav L. Shah[e–g]

[a]Department of Pulmonary Diseases, University of Groningen, University Medical Center Groningen (UMCG), Groningen, The Netherlands; [b]Groningen Research Institute for Asthma and COPD, University of Groningen, University Medical Center Groningen (UMCG), Groningen, The Netherlands; [c]Krankenhaus vom Roten Kreuz, Stuttgart, Germany; [d]Thoraxklinik and Translational Lung Research Center (TLRC), University of Heidelberg, Heidelberg, Germany; [e]Royal Brompton and Harefield NHS Foundation Trust, London, UK; [f]Chelsea and Westminster Hospital NHS Foundation Trust, London, UK; [g]National Heart and Lung Institute, Imperial College, London, UK

Medical history/co-morbidity
Avoiding significant airway disease (asthma, chronic bronchitis, bronchiectasis)
Pulmonary hypertension
Prior lung surgery

Inclusion
COPD according to GOLD, with FEV_1 <45% predicted
Presence of emphysema on HRCT scan, showing tissue destruction with percentage voxel density less than –950 HU between 20 and 80%
Severe hyperinflation assessed by body box: RV/TLC >58% and RV >200% predicted (absolute minimal criteria)
Dyspnoea scoring ≥2 mMRC
Optimal pharmacological and non-pharmacological treatment, including abstinence from smoking during at least 6 months, and a regular exercise programme
Fit enough to undergo the bronchoscopic procedure, including a 6-minute walking distance >140 m

Exclusion
Severe gas exchange abnormality: $PaCO_2$ >7.3 kPa (55 mm Hg) and/or PaO_2 <6.7 kPa (50 mm Hg) (room air)
Recurrent airway infections ≥3 times/year
Significant chronic bronchitis, including asthmatic bronchitis and Asthma COPD Overlap (ACO)
Radiological abnormalities like:
- Severe bronchial wall thickening
- Bronchiectasis
- Giant bullae >1/3 lung volume
- Significant presence of paraseptal emphysema
- Pulmonary nodules which are suspicious for lung cancer or active infection
- Significant fibrotic lesions and signs of interstitial lung disease
- Previous lung volume reduction surgery or lobectomy/pneumonectomy

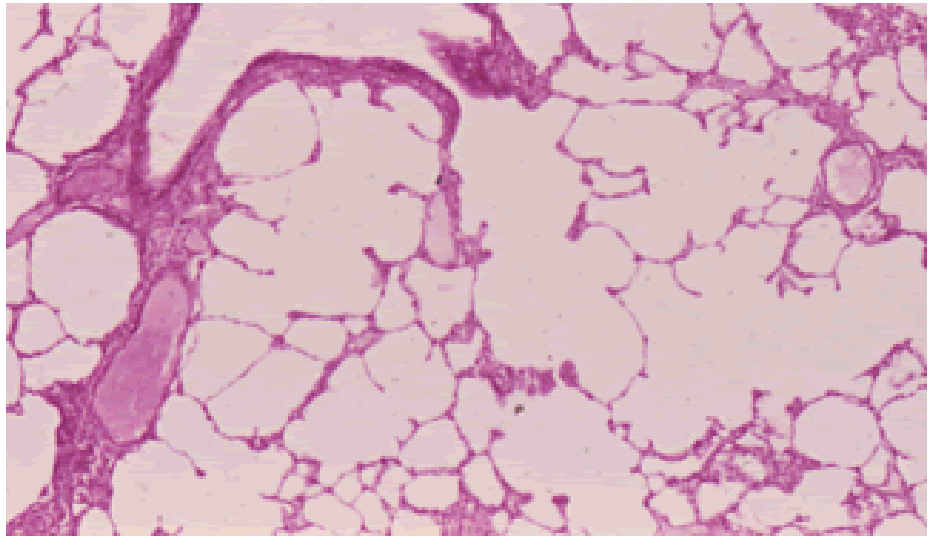
Pulmonary hypertension defined by right ventricular systolic pressure >50 mm Hg via echocardiogram
Evidence of other disease(s) which may compromise survival of the subject or reduce the benefits of coil treatment
Medication like antiplatelet or anticoagulant therapy which cannot be stopped prior to the procedure
Chronic immunomodulatory therapy; e.g. methotrexate or anti-TNF to treat an autoimmune disorder, prednisolone ≥10 mg/day, CVID (common variable immunodeficiency), maintenance antibiotics
Sensitivity or allergy to nickel or to drugs required to perform bronchoscopy

Pour les autres techniques

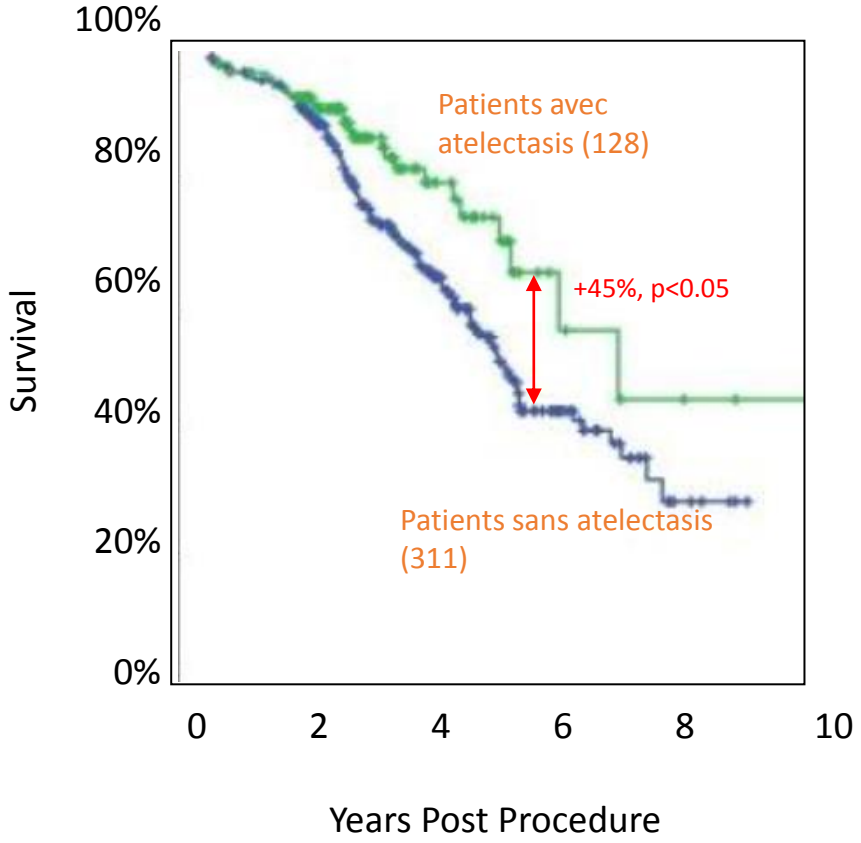
- Etudes françaises et internationales à promouvoir (vapeur, colle…)

- Déterminer les patients éligibles

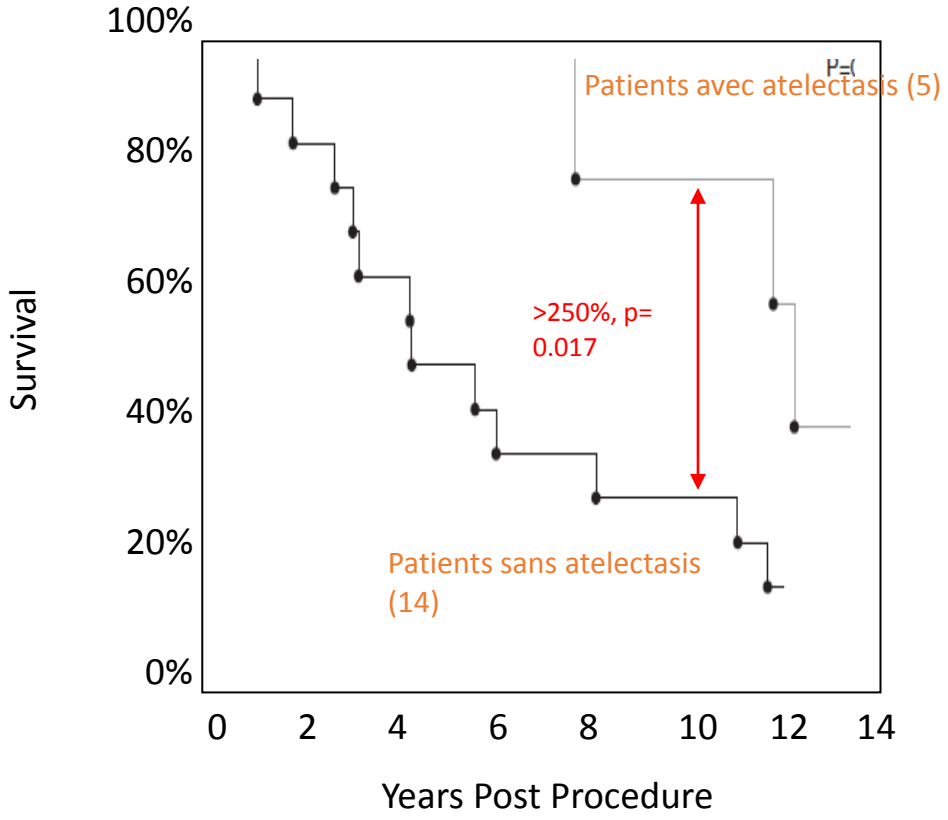
Réduction d’emphysème
Complications/survie



Bénéfices potentiels sur la survie



Gompelmann D et al. (2016) Eur Respir J



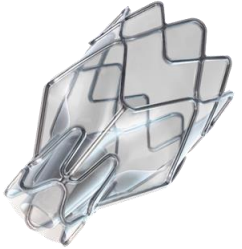
Hopkinson NS et al. (2016) Eur Respir J

Synthèse Résultats Valves

RCT	Number of Subjects / Follow-up period	Improvement in: Lung Function (FEV_1%) MCID = 10%-15%	Improvement in: Exercise Capacity (6MWD) MCID = 26 m	Improvement in: Quality of Life (SGRQ) MCID = -4 pts	SAE Pneumothorax Rate
VENT[4] (US + OUS)	n=122 (post-hoc subset) 6 months	24.8%	28 m	-8.4 pts	11.4%
BeLieVeR-HIFi[3]	n=50 3 months	20.9%*	33 m*	-5.1 pts	8.0%
STELVIO[2]	N=68 6 months	17.8%*	74 m*	-14.7 pts	18.0%
IMPACT[1]	n=93 3 months	17.0%*	40 m*	-9.6 pts*	25.6%

Source: 1. Valipour A, et al. Am J Respir Crit Care Med. 2016; 2. Klooster K. et al. N Engl J Med. 2015; 373: 2325-36 + Supplementary Appendix; 3. Davey C et al, Lancet. 2015; 386 (9998): 1066-73 + Supplementary appendix; 4. Scuirba F.C. et al. N Engl J Med. 2010; 363(13): 1233-44/ Herth F. J. et al. Eur. Respir. J. 2012; 39(6): 1334-42/ Ad hoc analysis on file at Pulmonx 5. Pulmonx data on first 75 patients, submitted to ATS as abstract

Synthèse Résultats Valves



RCT	Design	Sample size & Follow-up period	Difference EBV vs Control Groups		
			Lung Function (FEV_1%) MCID = 10%-15%	Exercise Capacity (6MWD) MCID = 26 m	Quality of Life (SGRQ) MCID = - 4 pts
LIBERATE[1] NEW	2:1 Randomization **Heterogeneous only** Multi-Center	n=190 12 months	**18.0 %***	**39.3 m***	**-7.1 pts***
TRANSFORM[2]	2:1 Randomization **Heterogeneous only** Multi-Center	n=97 6 months	29.3 %*	79 m*	-6.5 pts*
IMPACT[3]	1:1 Randomization **Homogeneous only** Multi-Center	n=93 6 months	16.3 %*	28 m*	-7.5 pts*
STELVIO[4]	1:1 Randomization **Heterogeneous & Homogeneous** Single Center	n=68 6 months	17.8 %*	74 m*	-14.7 pts

Complications of endobronchial valve treatment can include but are not limited to pneumothorax, worsening of COPD symptoms, pneumonia, dyspnea and, in rare cases, death.

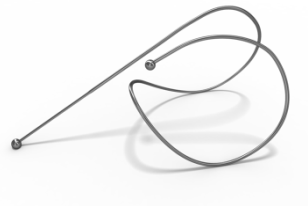
* Intent-to-Treat population

[1] Criner et al. Am J Resp Crit Care Med.2018, in press | [2] Kemp S et al. Am J Resp Crit Care Med 2017; (196)12: 1535-1543 | [3] Valipour et al. Am J Respir Crit Care Med. 2016; Vol 194, Iss 9, pp 1073-1082 and Data on file at Pulmonx | [4] Klooster K. et al. N Engl J Med. 2015; 373: 2325-2336 + Supplementary Appendix

Complications pour les valves

- **Pneumothorax (15%-25%)**
  - habituellement < 24h, >85% dans les 4er jours
- **Pneumonie (<5%)**
- **Exacerbation (4-10%)**
  - Irritation de l'arbre bronchique post-implantation
- **Granulation (5%)**
  - Toux persistante
  - Causes fuite et échec atélectasie
- **Expectoration des valves (<5%)**

Objectif principal



Augmentation du PM6 ≥ 54 m à 6 mois

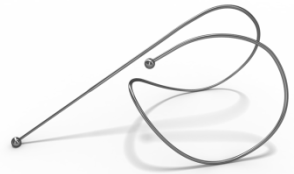
	No. Coil/SOC	Coil Treatment	SOC	p value
Intention-to-treat, No. (%)	44/44	16 (36)	8 (18)	0.028
Per protocol, No. (%)	42/44	16 (38)	8 (18)	0.02
Maximum non-response bias, No. (%)	50/50	16 (32)	8 (16)	0.03

The study was powered for the 6-month endpoint.

Le traitement par coils est supérieur aux SoC pour l'augmentation de la capacité à l'exercice à 6 mois, dans l'emphysème sévère

Deslée G, Mal H, Dutau H, Bourdin A, Vergnon JM, Pison C, Kessler R, Jounieaux V, Thiberville L, Leroy S, Marceau A, Laroumagne S, Mallet JP, Dukic S, Barbe C, Bulsei J, Jolly D, Durand-Zaleski I, Marquette CH; REVOLENS Study Group. Lung Volume Reduction Coil Treatment vs Usual Care in Patients With Severe Emphysema: The REVOLENS Randomized Clinical Trial. JAMA. 2016 Jan 12;315(2):175-84.

Objectifs secondaires



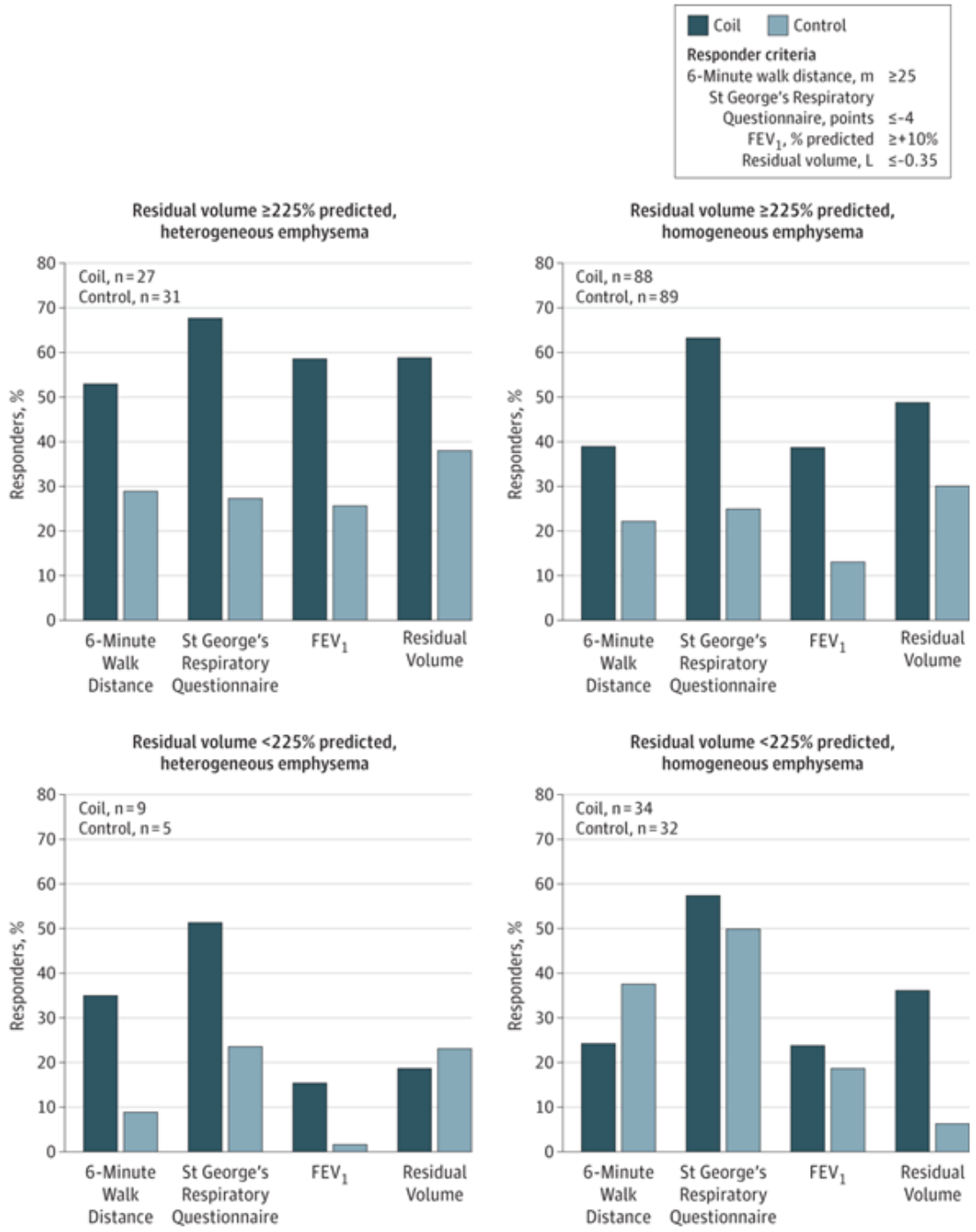
Le traitement par coils est associé à une augmentation durable (6 et 12 mois) de la fonction pulmonaire, de la dyspnée et de la qualité de vie

Value (SD)	Coil Treatment vs. SOC	p	Coil Treatment vs. SOC	p
6MWT, m	+ 21m	0.048	+21m	0.09
mMRC, pts	- 0.4	0.014	- 0.4	0.023
FEV_1, %	+ 12%	0.001	+ 11%	0.002
FVC, %	+ 10%	0.015	+ 10%	0.023
RV, %	- 7%	0.009	- 7%	0.003
SGRQ, pts	- 13.4	<0.001	-10.6	<0.001
	6 months		**12 months**	

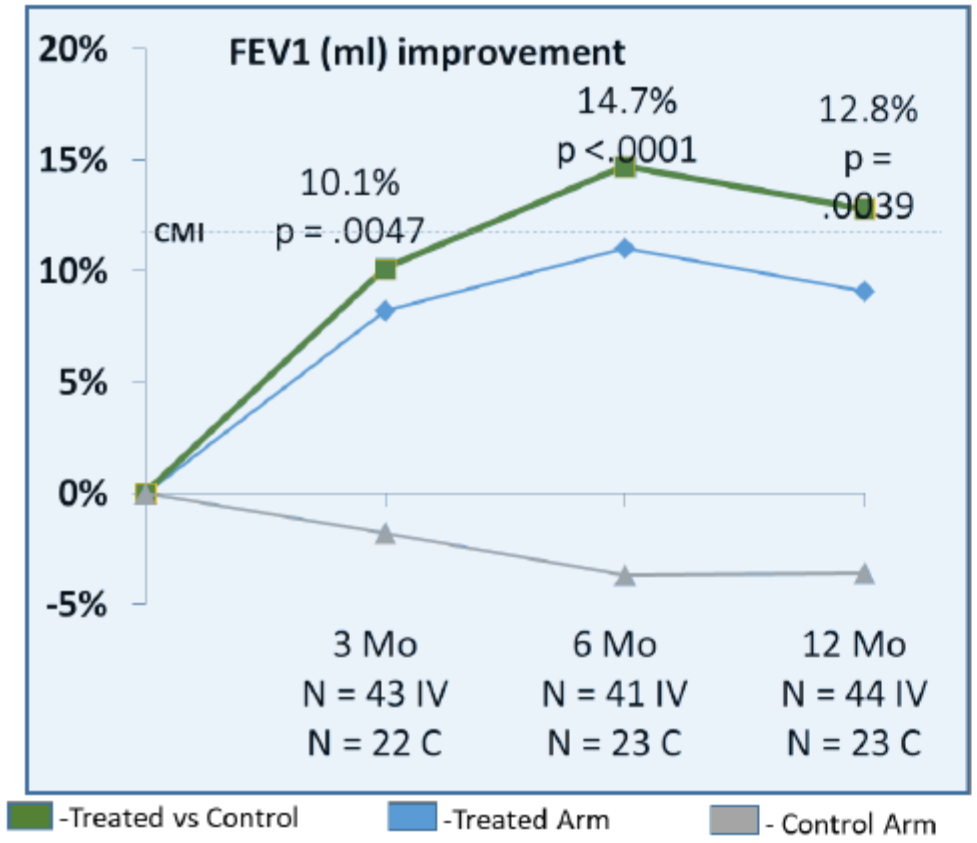
Deslée G, Mal H, Dutau H, Bourdin A, Vergnon JM, Pison C, Kessler R, Jounieaux V, Thiberville L, Leroy S, Marceau A, Laroumagne S, Mallet JP, Dukic S, Barbe C, Bulsei J, Jolly D, Durand-Zaleski I, Marquette CH; REVOLENS Study Group.. Lung Volume Reduction Coil Treatment vs Usual Care in Patients With Severe Emphysema: The REVOLENS Randomized Clinical Trial. JAMA. 2016 Jan 12;315(2):175-84.

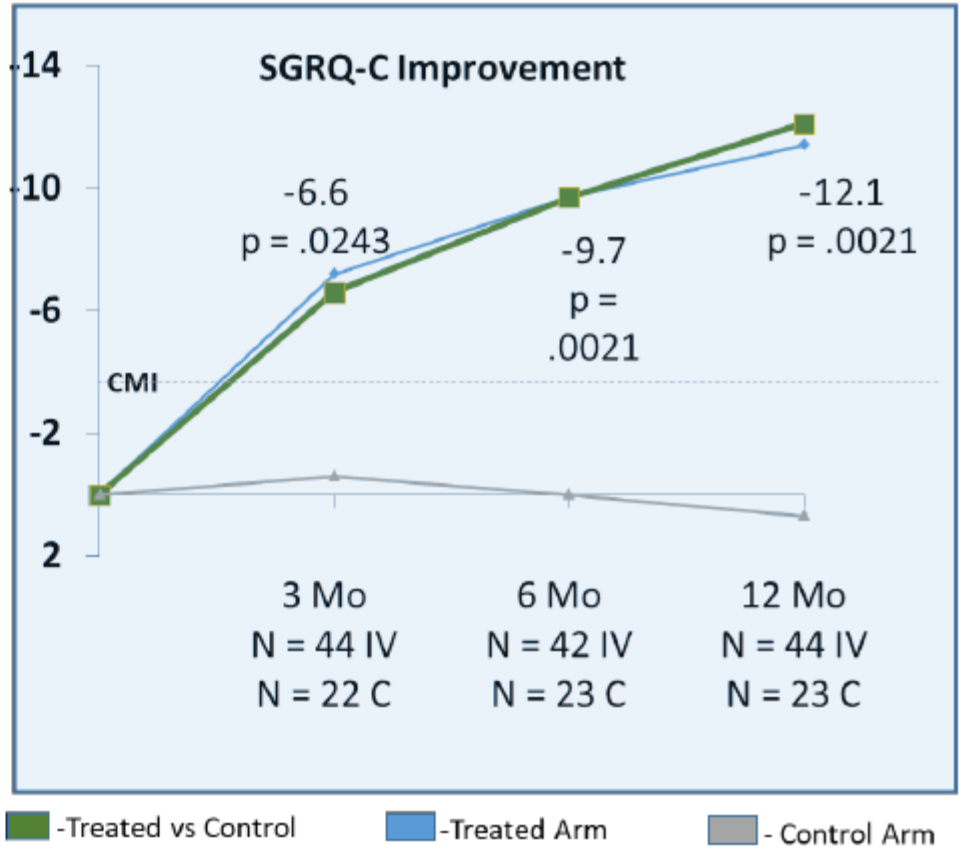
RENEW

Résultats selon homogénéité de l'emphysème et le VR



STEP-UP résultats vapeur





Herth, et. al, *Lancet Respir Med 2016*

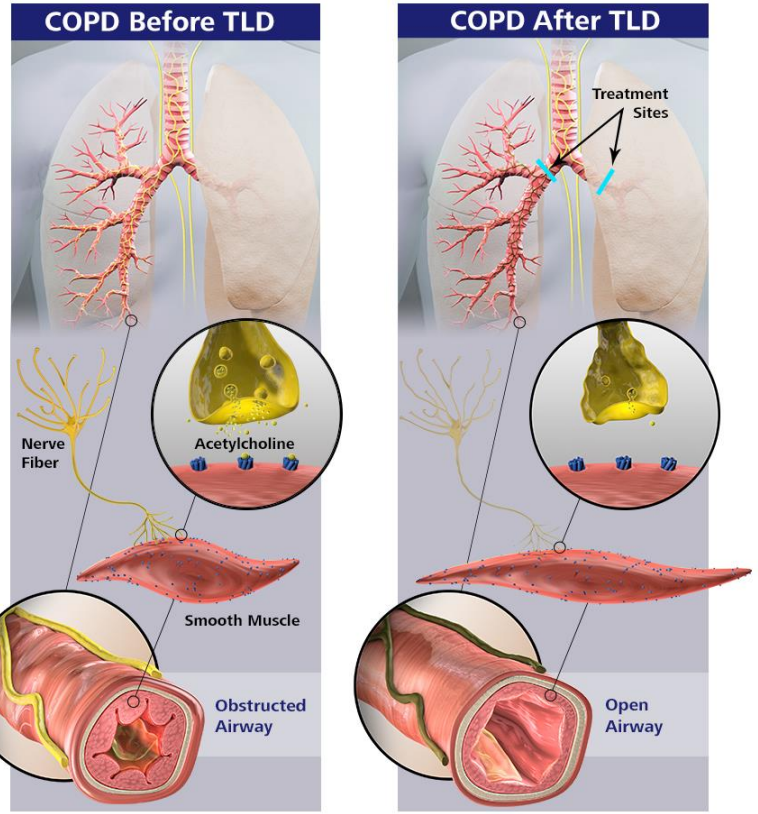
Shah, P. L., et al *The Lancet Respiratory Medicine*, 2016

STEP-UP complications vapeur

CV+ and CV- Patients	Treatment Arm (45 patients)		Control Arm (24 patients)	
	0-180 days after treatment - N (%)	181-360 days after treatment - N (%)	0-180 days after random - N (%)	181-360 days after random - N (%)
Exacerbation	11 (24%)	7 (16%)	1 (4%)	2 (8%)
Pneumonia/Pneumonitis	8 (18%)	0 (0%)	2 (8%)	2 (8%)
Pneumothorax (asymptomatic)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Complications Requiring:				
Surgery	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Chest tube(s)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Re-bronchoscopy	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ICU-stay	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hemoptysis	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Death	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Any RSAE	16 (36%)	7 (16%)	3 (13%)	4 (17%)

* Patient death 87 days after treatment secondary to COPD exacerbation and influenza.

Bronchodilatation permanente



Dénervation du Vague par Radio-fréquence

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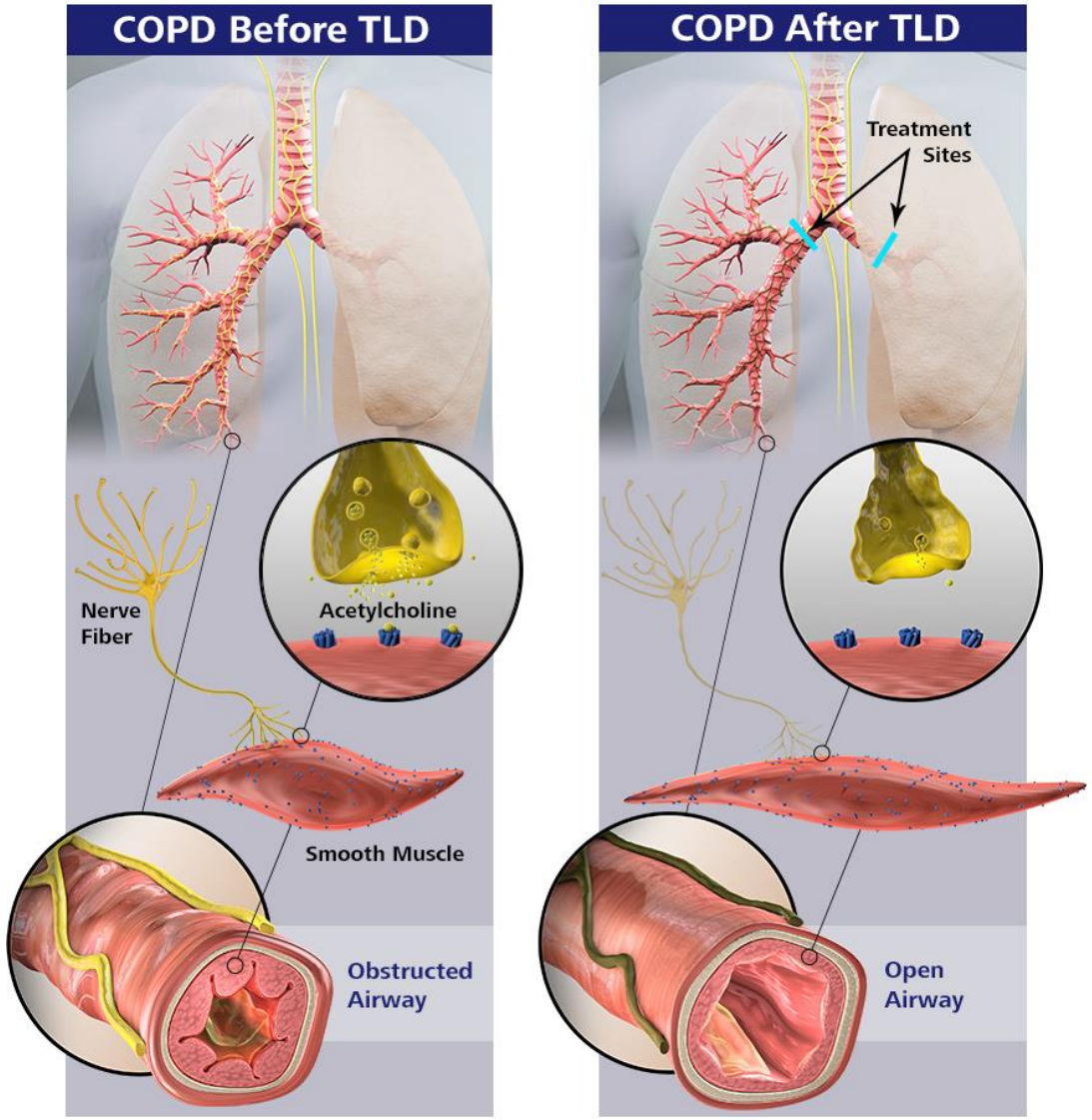
Figure 3: dNerva Balloon

La dénervation par radio-fréquence

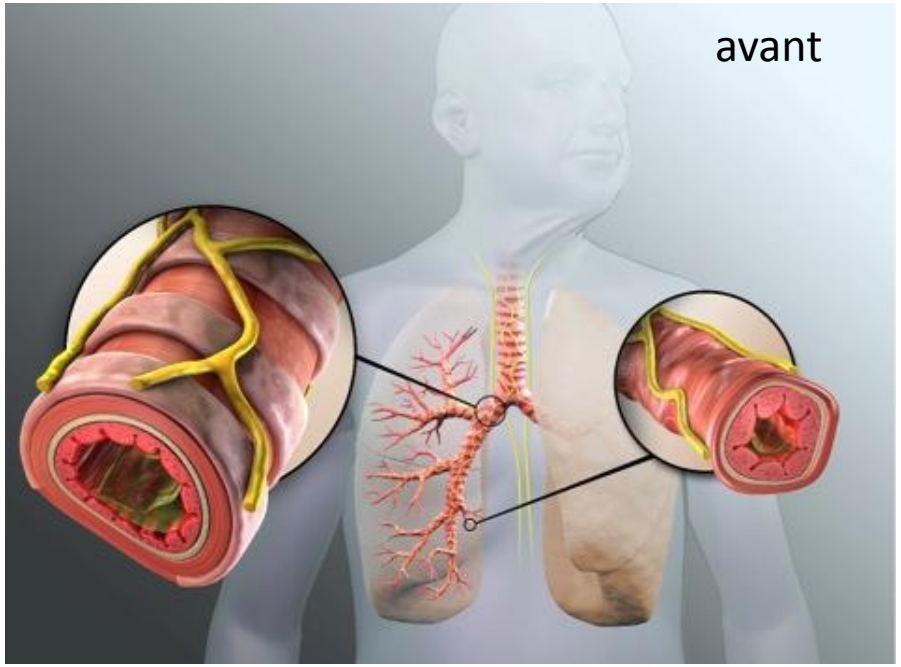


- Muscles lisses hypertrophiés dans paroi bronchique
- hypersécrétion de mucus
- nerfs le long des BP et suivantes

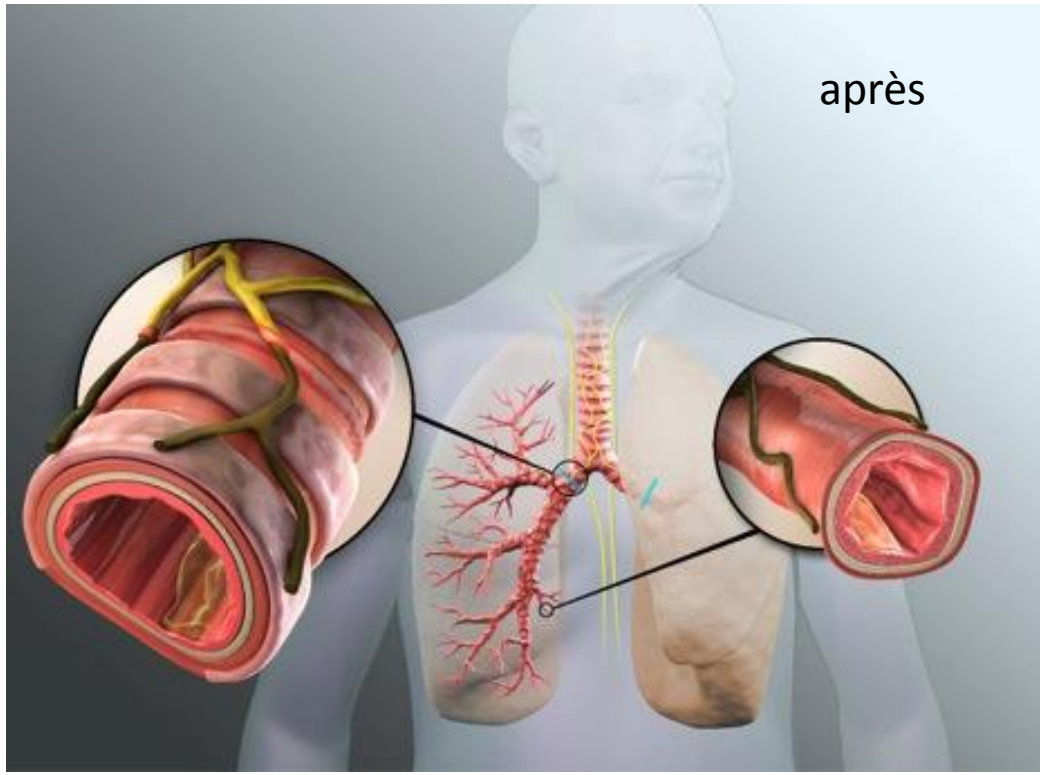
•Acétylcholine, principal neurotransmetteur du système para-sympathique

-> Bronchoconstriction et inflammation, mucus via les récepteurs muscariniques

NUVAIRA™



- Traitement bilatéral
- Circonférentiel
- Dans les deux bronches principales
- Sous AG et scopie



- **Diminution de l'hyperactivité des nerfs respiratoires** (système parasympathique) contribuant à l'obstruction pulmonaire, la survenue et la sévérité des exacerbations :
  - Réduction importante de la libération neuronale d'acétylcholine au niveau des cellules musculaires et glandulaires bronchiques, grâce à la radiofréquence.
- **A court terme :** bronchodilatation permanente et durable, réduction de la sécrétion de mucus.
- **Objectif à long terme :** stabilisation de la fonction respiratoire, avec réduction de la fréquence et de la sévérité des exacerbations de BPCO par rapport au traitement pharmacologique optimal réalisé seul.

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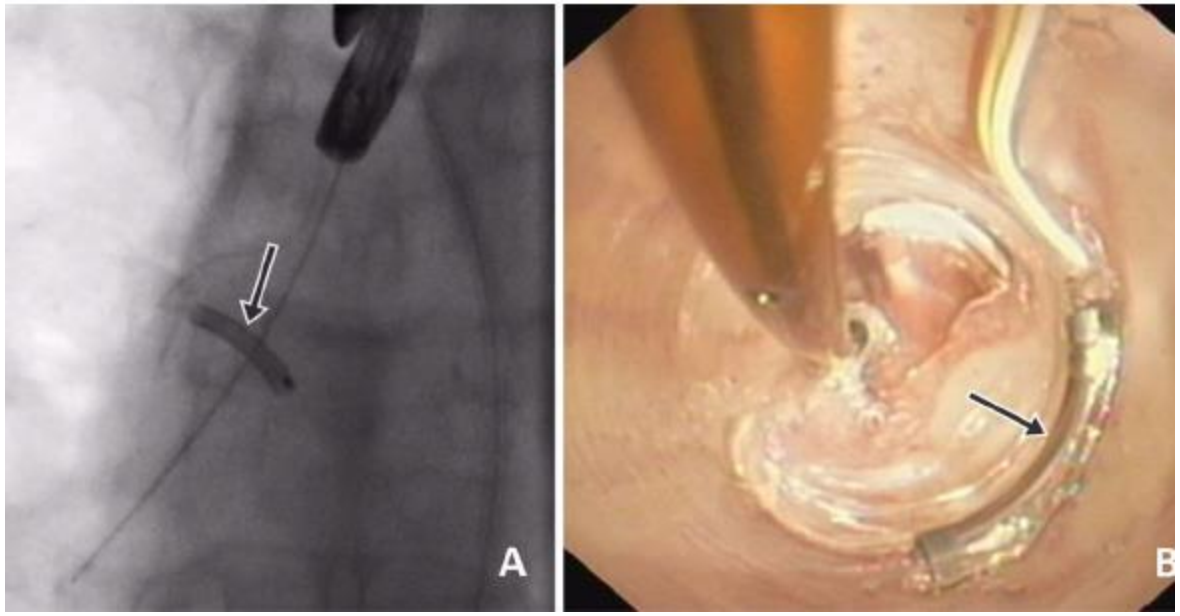
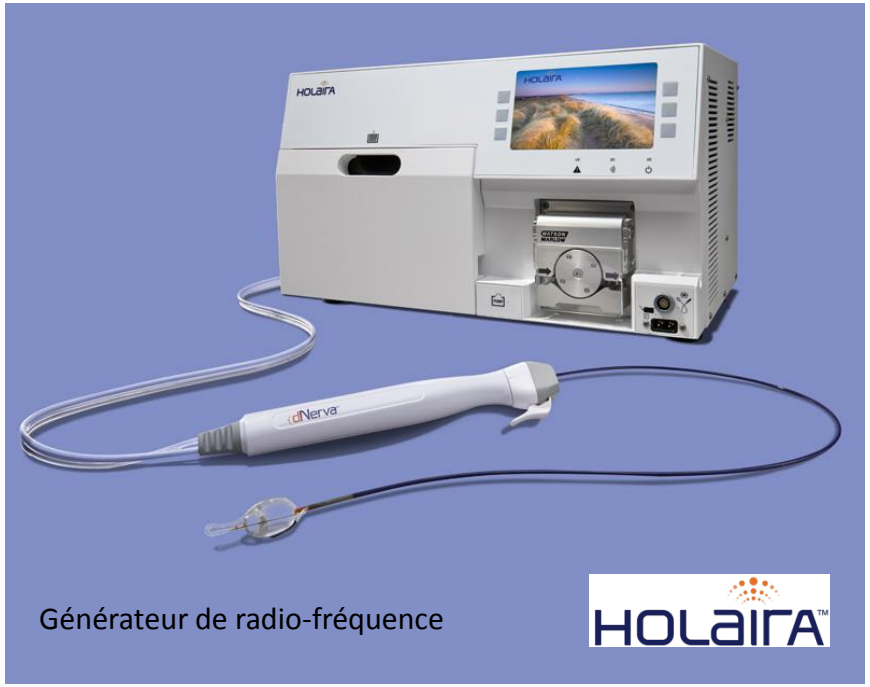
Figure 3: dNerva Balloon

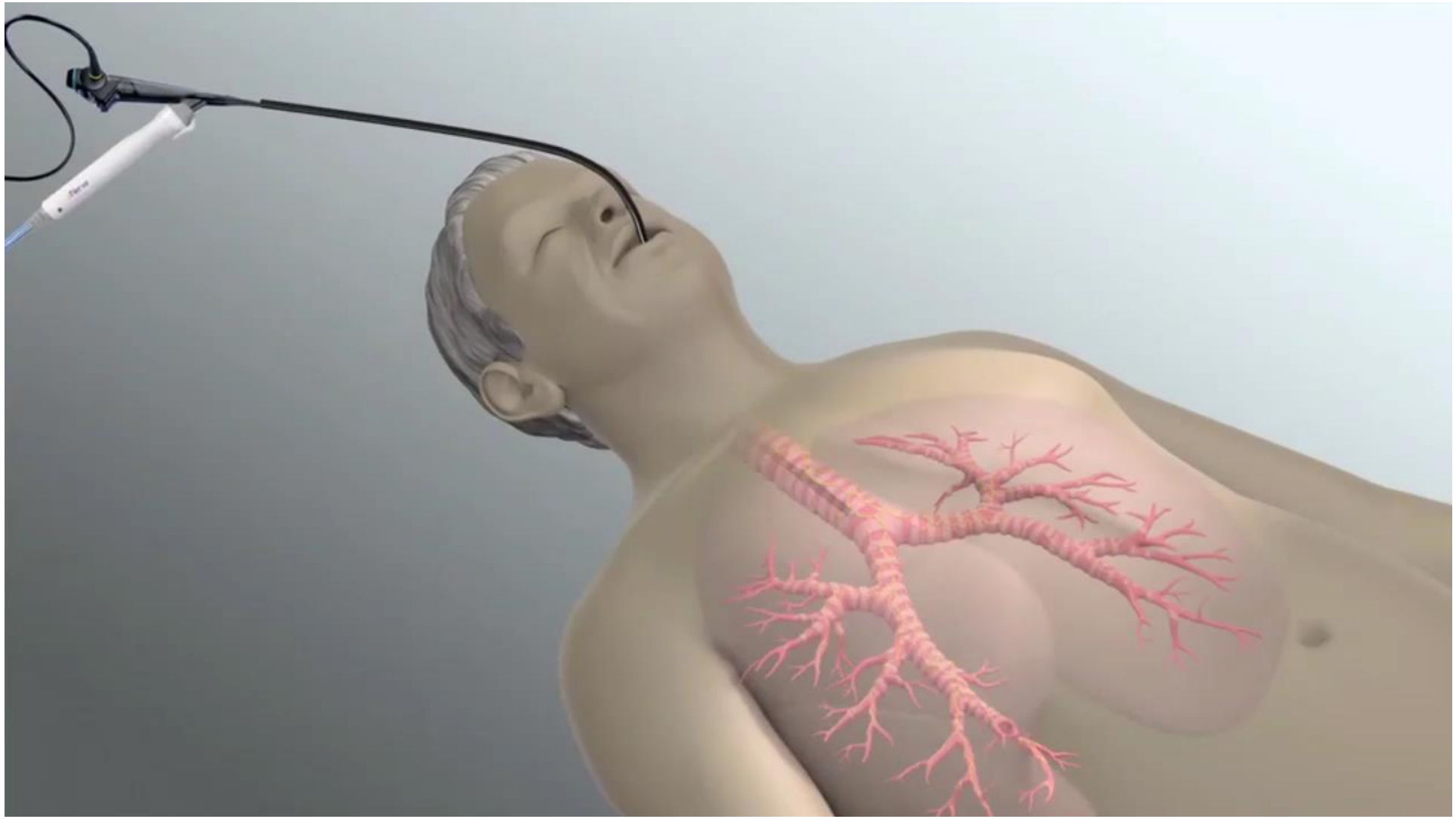




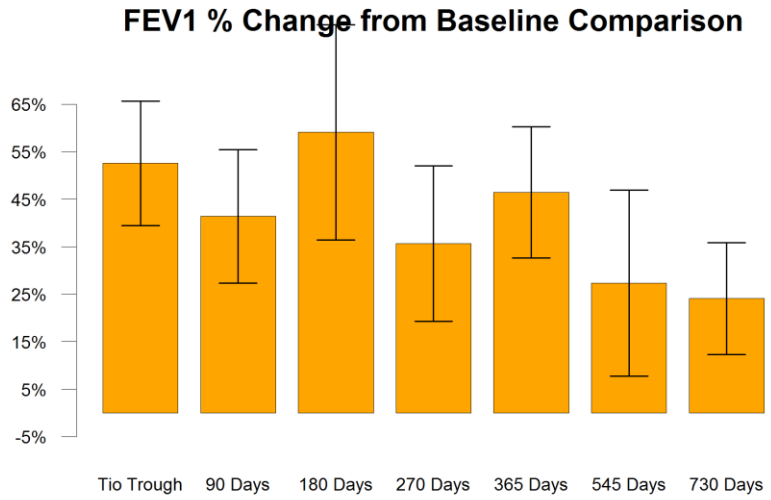
Générateur de radio-fréquence

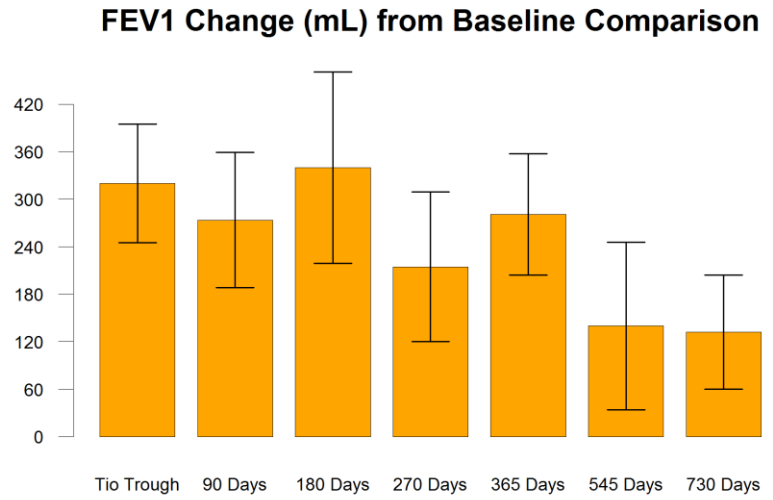
Figure 2: dNerva Catheter (with bronchoscope)

Slebos DJ, Klooster K, Koegelenberg CF, Theron J, Styen D, Valipour A, Mayse M, Bolliger CT.
Targeted lung denervation for moderate to severe COPD: a pilot study. Thorax. 2015 May;70(5):411-9.



IPS-II (15W) : effets à long-terme





Persistance d'une amélioration de 120 mL à 2 ans

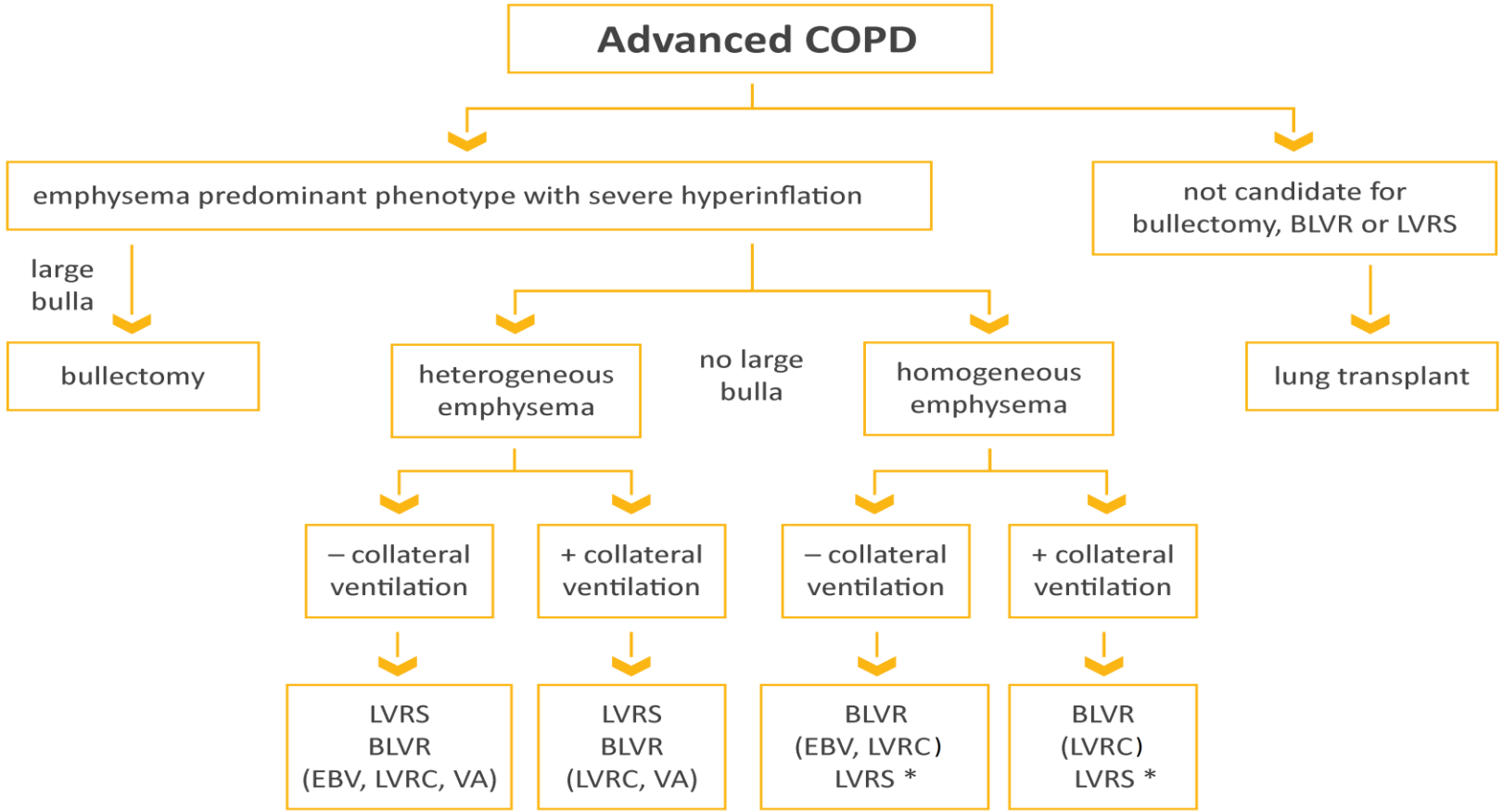
RF sans LAMA comparée à la baseline

Développement clinique international

	IPS et IPS-II	AirFlow 1	AirFlow 2	AirFlow 3
Phase	Phase I+	Phase IIA	Phase IIB	Phase III
Version de Nuvaira	Génération 1	Génération 2	Génération 2	Génération 2
Type d'étude	Registre	Etude randomisée	Etude randomisée (avec intervention « *sham* »)	Etude randomisée (avec intervention « *sham* »)
Effectif	37	46	82	~ 400
Objectifs :				
Faisabilité	✔			
Procédure	✔	✔		
Dose de RF	✔	✔		
Sécurité	✔	✔	✔	✔
Efficacité			✔	✔
Etat d'avancement	Résultats à un an publiés	Résultats à un an disponibles	En phase *cross-over*. Résultats soumis pour publication.	Protocole en cours de validation FDA

INTERVENTIONAL BRONCHOSCOPIC AND SURGICAL TREATMENTS FOR COPD

Overview of various therapies used to treat patients with COPD and emphysema worldwide. Note that all therapies are not approved for clinical care in all countries. Additionally, the effects of BLVR on survival or other long term outcomes or comparison to LVRS are unknown.



Definition of Abbreviations: BLVR, Bronchoscopic Lung Volume Reduction, EBV, endobronchial Valve, LVRS, Lung volume reduction surgery, LVRC, Lung volume reduction coil, VA, Vapor ablation

*at some but not all centers

FIGURE 4.5

En conclusion

- Réduction d'emphysème par voie endoscopique en plein développement
  - Valves VEMS < 50%, VR > 175% : Remboursement fin 2019, actuellement COMEDIM
  - Spirales VR > 200% : étude ELEVATE
  - Vapeur : STEP-UP French
  - Colle en attente de protocole
- Bronchodilatation permanente (dénervation par radiofréquence)
  - 40-75 ans
  - VEMS > 30%
  - Reprise courant 2019 d'AIRFLOW 3
- Importance de la sélection des patients
- Résultats sur le long terme en cours d'évaluation mais prometteur avec validation des valves et des spirales, résultats AIRFLOW-(1 , 2 puis 3) prometteurs

Merci de votre attention

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