Non pharmacological management of COPD

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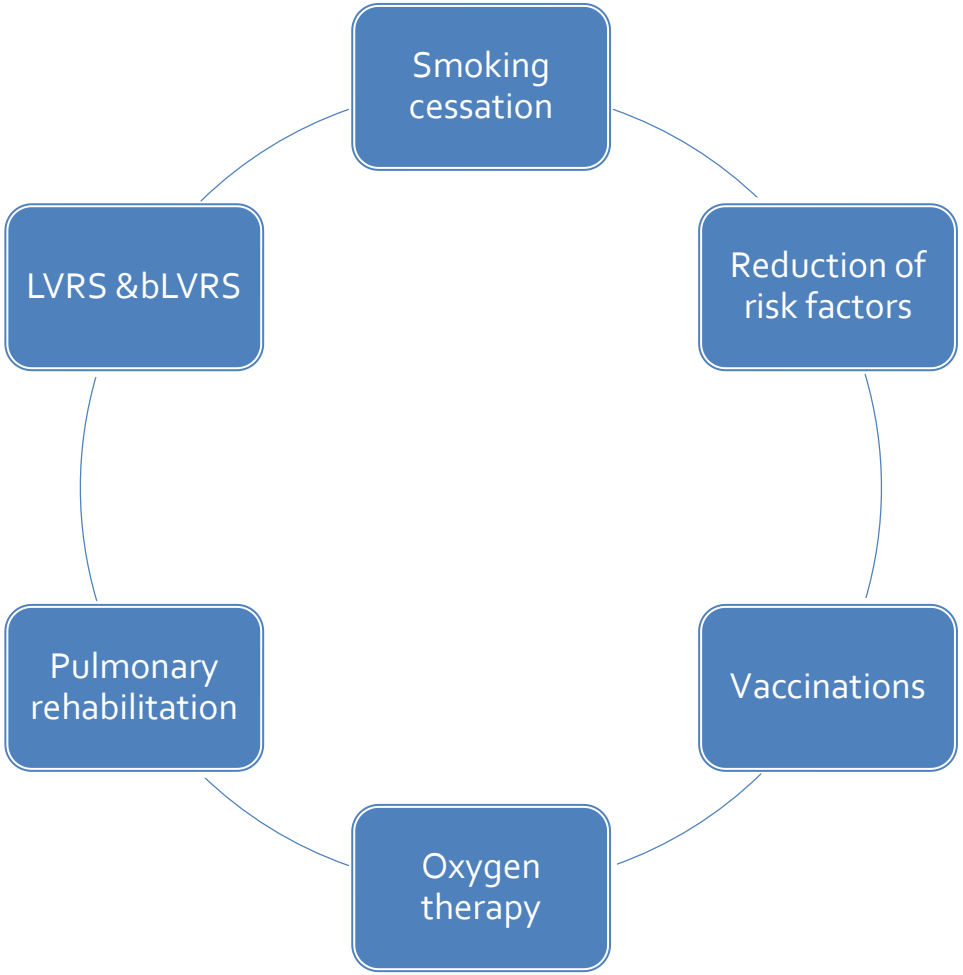
19 Jan 2018

Aim of treatment in COPD

- Improve symptoms
- Decrease exacerbations
- Improve patient function and quality of life

Non pharmacological management



Smoking cessation – will it help ?

- Yes
- Reduces rate of decline in FEV1

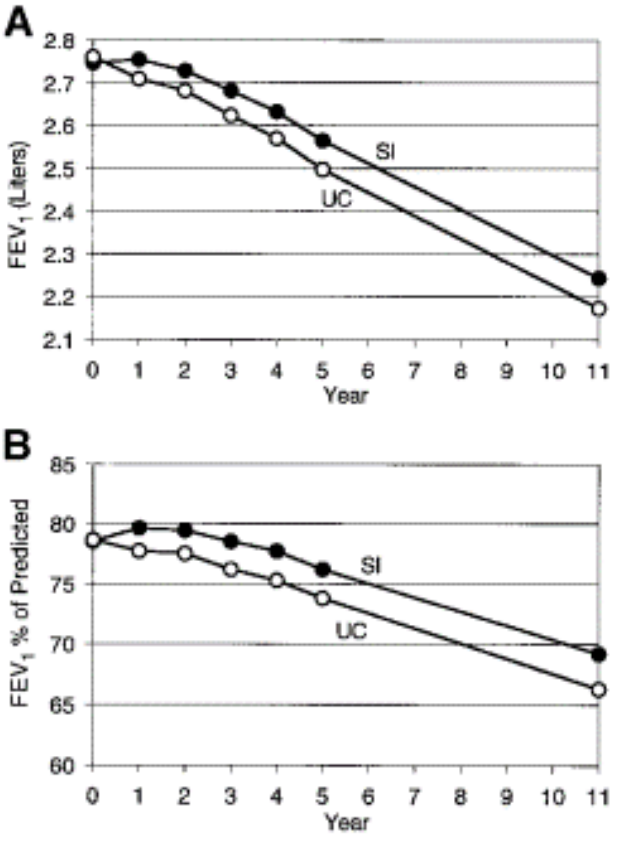
- Lung health study,
  - rate of decline in FEV1 (ml/yr) over 11 yrs

	Quit smoking	Continued smoking
Male	30.2	66.1
Female	21.5	54.2

Anthonisen NR et al Am J Respir Crit Care Med. 2002 Sep 1;166(5):675-9

Smoking cessation

- FEV1 in SI
  - Declined by 502 ml
  - 9.3% of predicted
- FEV1 in UC
  - Declined by 587 ml
  - 12.3% of predicted



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Smoking cessation

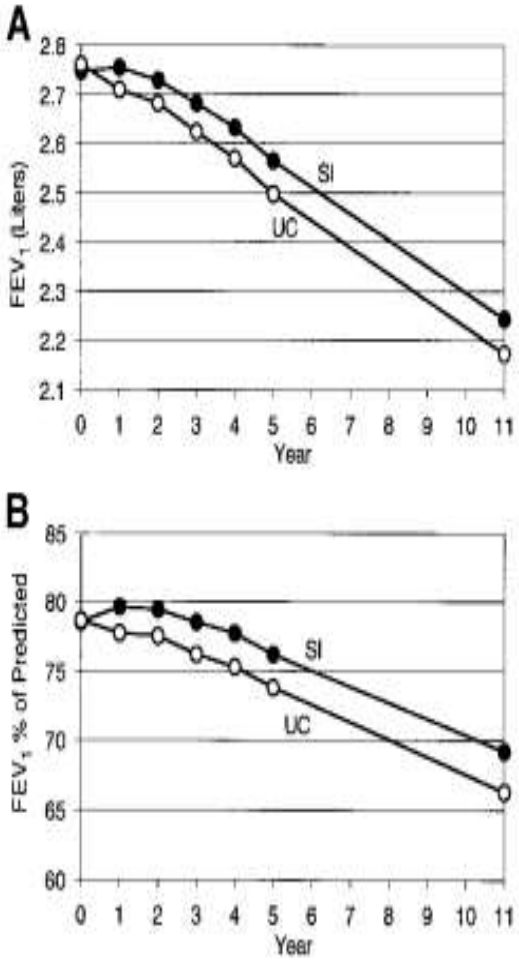


Figure 1. Loss of lung function among LHS 3 enrollees over the 11 years of study of the SI group (*closed symbols*) and the UC group (*open symbols*). Average values of post-bronchodilator FEV_1 are shown, expressed in absolute terms in (*A*) and as a percentage of the predicted normal value in (*B*).

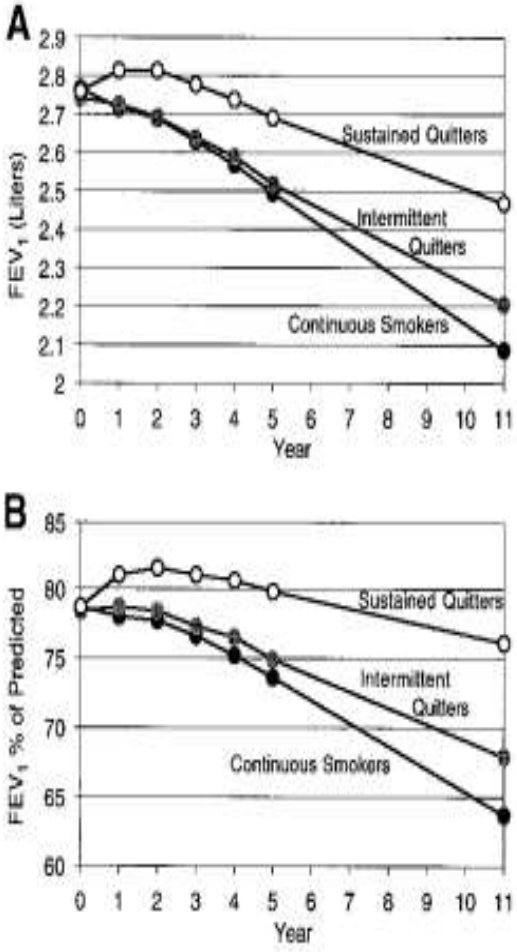


Figure 2. Loss of lung function over the years of study among sustained quitters (*open symbols*), continuing smokers (*closed symbols*), and intermittent smokers (*gray symbols*). Average values of post-bronchodilator FEV_1 are shown, expressed in absolute terms in (*A*) and as a percentage of the predicted normal value in (*B*).

Anthonisen NR et al Am J Respir Crit Care Med. 2002 Sep 1;166(5):675-9

Smoking cessation

- Clinical advise
- Encouragement
- Nicotine replacement therapy
- Behavioural counselling

Smoking cessation - modalities

- 5 step algorithm
  - Ask
  - Advise
  - Assess
  - Assist
  - Arrange

Smoking cessation

- Ask
  - Implement an officewide system that ensures that, for every patient at every clinic visit, tobacco use status is queried and documented
- Advise:
  - Strongly urge all tobacco users to quit in a clear, strong, personalized manner
- Assess:
  - Determine the patient's willingness to quit smoking within the next 30 days
- Assist:
  - Provide aid for the patient to quit
- Arrange:
  - Schedule follow-up contact, either in person or by telephone
  - 1 wk and 1 month

Alternatives

- Financial incentives
  - A RCT among 2538 smokers employed at a company in the US found that a substantial financial incentive (as much as $800) increased smoking cessation rates
  - Rates of sustained abstinence from smoking through 6 months were higher with each of the four incentive programs (range, 9.4 to 16.0%) than with usual care (6.0%) ($P<0.05$)[1]
- Acupuncture
  - Acupuncture is included in some commercially available smoking cessation programs
- Aversive therapy

1- Halpern SD et al N Engl J Med. 2015 May 28;372(22):2108-17

More practical

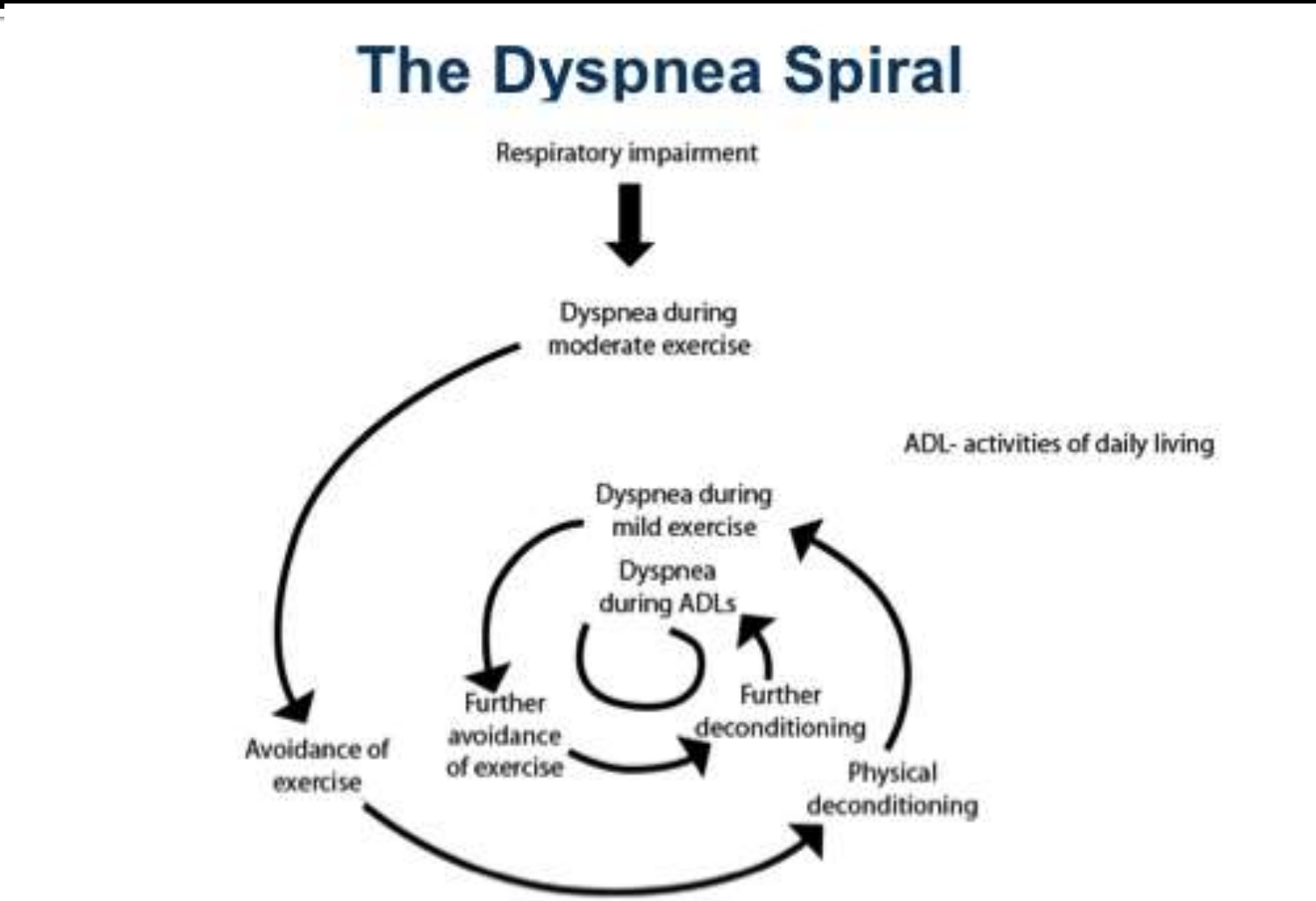
- In systematic analysis of 8 RCT evaluating smoking interventions for COPD pts
- Counselling and pharmacotherapy was more effective than each strategy separately
- No difference with
  - Intensity of counselling
  - Choice of pharmacotherapy

Warnier MJ et al Eur Respir J. 2013 Mar;41(3):727-34

Pulmonary rehabilitation

- Whom ?
- All stages of COPD who are symptomatic
- No justification for selection on basis of age, impairment, disability, smoking status or oxygen use
- Continuing smokers may not be eligible and less likely to complete
- Contraindicated if recent MI/unstable angina

SPIRAL OF DISABILITY



Haas F, et al. In: Casaburi R, Petty TL, eds. *Principles and Practice of Pulmonary Rehabilitation*. Philadelphia, Pa; Saunders; 1993.

Pre-programme evaluation

- Control of symptoms of cough and fatigue:
  - Real time eval.: MRC breathlessness & Borg dyspnea scale
  - Recall of symptoms
- Performance evaluation:
  - Directly observed or self reported : PFTs, ABG or Oximetry
- Exercise tolerance:
  - 6 minutes walking test
  - Cardiopulmonary exercise testing
- Quality of life: (specific or non-specific)
  - Chronic respiratory disease questionnaire & SGRQs
  - SF- 36
- Assessment of respiratory and peripheral muscle strength
- Nutritional assessment
  - History, Laboratory, Anthropometry

Setting

- Hospital/ outpatient/ home
- Mostly outpatient based

- Outpatient – 2-3 days/ wk
- Inpatient - 5 days/ wk

- Home based rehab programmes – comparable results

Home based rehab

- RCT of 166 pts
- Home based rehab Vs OPD based
- Centre based pulmonary rehabilitation was an 8-week, twice weekly OPD based supervised programme
- Home-based pulmonary rehabilitation commenced with one home visit by a physiotherapist to establish exercise goals, assess inhaler technique and supervise the first exercise session
- 6 MWT & CRQ were similar

Holland AE et al Thorax. 2017 Jan;72(1):57-65

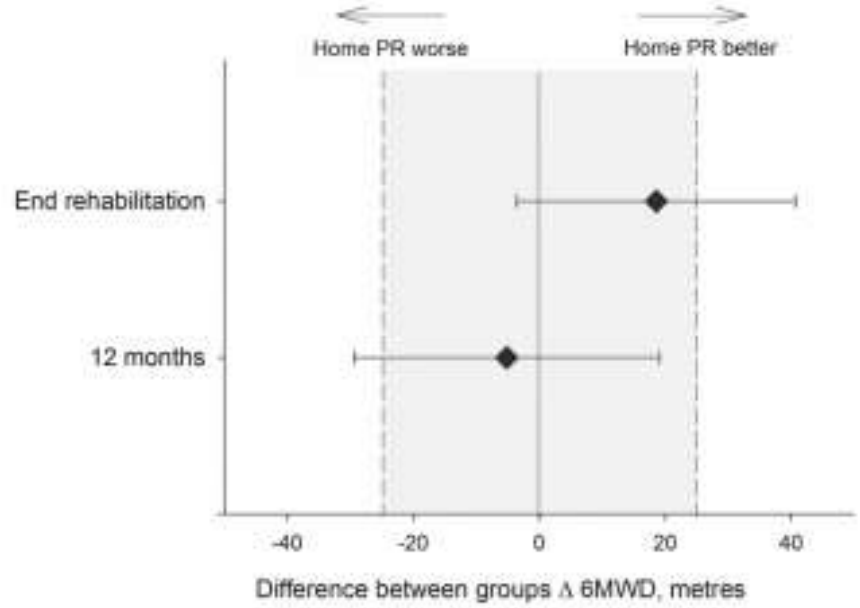


Figure 2 Difference between groups for 6 min walk distance (6MWD) and equivalence limits. PR, pulmonary rehabilitation. Data are mean and 95% CI for difference between groups. Shaded area represents equivalence limits, which are ±minimal important difference.

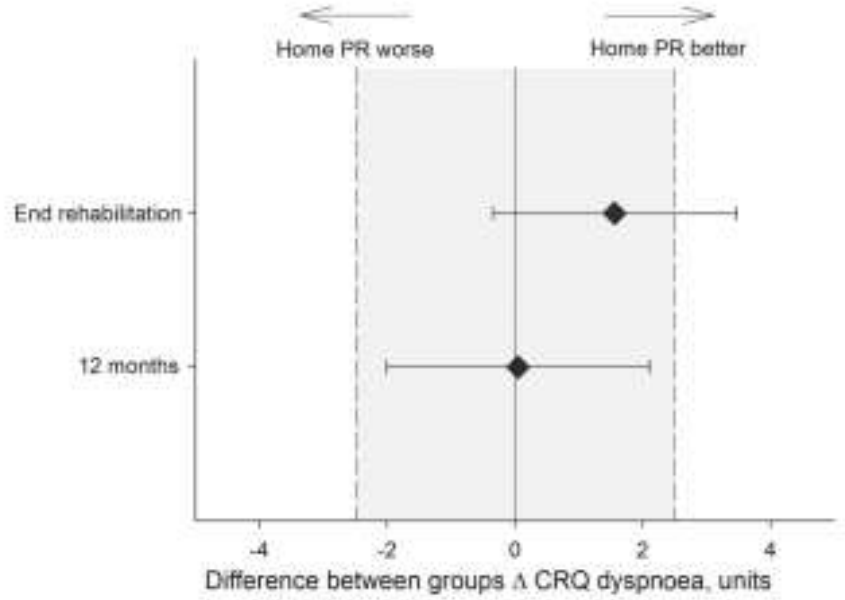


Figure 3 Difference between groups for Chronic Respiratory Disease Questionnaire (CRQ) dyspnoea domain and equivalence limits. PR, pulmonary rehabilitation. Data are mean and 95% CI for difference between groups. Shaded area represents equivalence limits, which are ±minimal important difference.

Holland AE et al Thorax. 2017 Jan;72(1):57-65

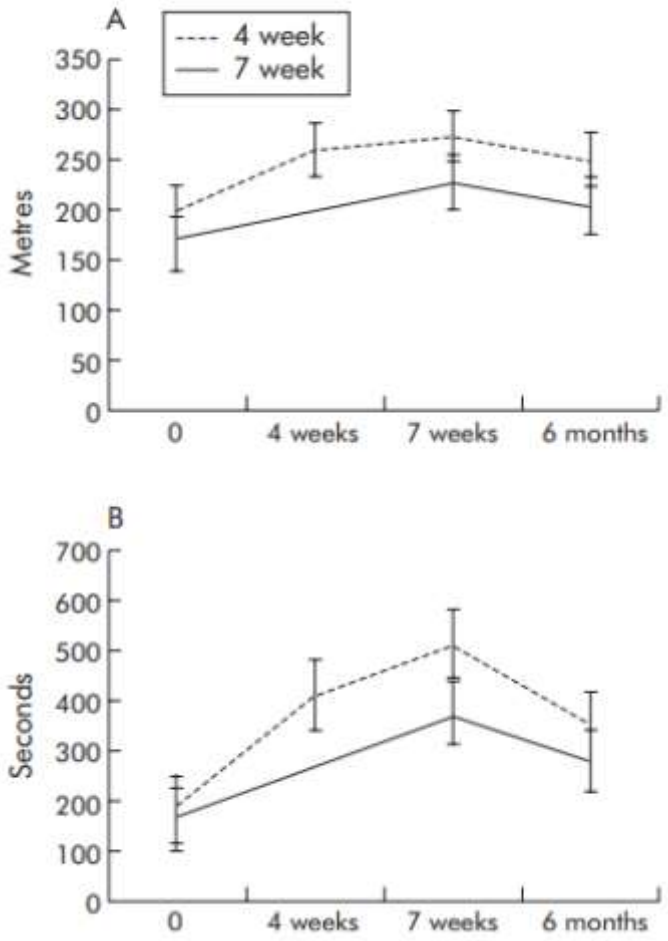
Duration

- 4 – 12 wks
- Longer duration – most of the programmes

- Improvement in exercise capacity plateaus at 12 wks of starting rehab programme

RCT – 4 Wk Vs 7 Wk

- 100 pts
- Outcomes measured were ISWT/ESWT/CRQS
- No statistically significant differences



Sewell L et al Thorax. 2006 Sep;61(9):767-71

Exercise - ??

Exercise training

- Endurance, resistance
- Continuous, interval

Exercise training – Endurance

- Endurance training –
- Conditioning
- Training loads > loads pt experiences in daily life
- At 60 – 70 % of individuals maximal work rate
- 3-5 times/Wk for 20-30 min
  - ATS-ERS recommends endurance exercise
    - (Am J Respir Crit Care Med. 2013 Oct;188(8):e13-64)

Exercise training – Strength

- Resistance/ Strength training
- Improves muscle mass
- Individual muscle groups are trained by repetitive lifting of weights
- Causes lower O_2 consumption and MV → evokes less dyspnea
  - advantageous for patients who are less tolerant of endurance training

Exercise – Does not improve lung mechanics or gas exchange, but optimizes other body systems

- Muscle biochemistry
  - higher work rates with less lactic acidosis leading to decreased ventilatory demand
- Reduced dynamic hyperinflation through reduced ventilatory demand
- Desensitization to dyspnea:
  - antidepressant effect, social interaction, self management, and adaptive behaviours

Casaburi, R and Z W allack. N Engl J Med 2009; 360:1329-1335

Exercise – reduces dyspnea

- At same level of physical work (watts) before and after rehabilitation
  - patients who underwent exercise training had a **lower RR, lower MV** and **less dynamic lung hyperinflation**
- This allowed them to perceive less dyspnea and to increase their exercise endurance

Porszasz J et al Chest. 2005;128(4):2025

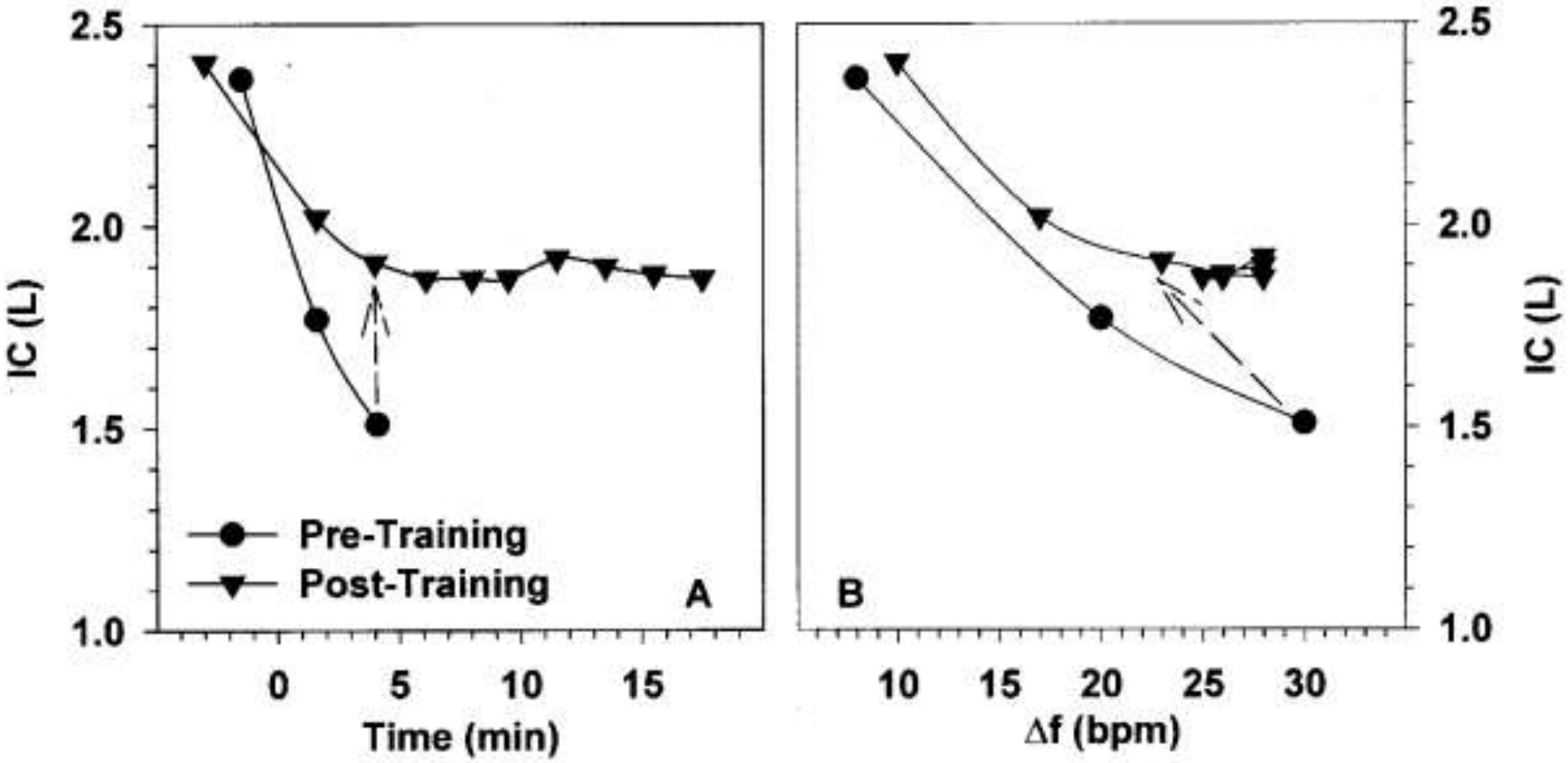


FIGURE 3. Changes in IC as a function of time (*left*, *A*) and of *f* (*right*, *B*) during CWR exercise prior to and after the training program in a representative subject. The dashed arrows connect the isotime values.

Porszasz J et al Chest. 2005;128(4):2025

Lower extremity exercise

- Foundation of pulmonary rehabilitation
  - Multiple controlled studies show:
    - Increased exercise tolerance
    - Walking distance
    - Dyspnea scores
    - QOL scores

Lower extremity exercises

- Walking
- Treadmill
- Stationary bicycle
- Stair climbing
- Sit & Stand

UPPER EXTREMITY EXERCISE

- Less data regarding exercise conditioning
- Some muscle groups serve dual function
  - Respiratory and postural
  - Upper Extremity training results in decreased ability for these muscles to participate in ventilation
- Evidence to support improvement in task specific performance

UPPER EXTREMITY EXERCISE

- Arm cycle ergometer
- Unsupported arm lifting
- Lifting weights

Upper extremity exercises

- RCT of 50 pts

- UEET plus PR Vs PR
- UEET
  - 15 sessions of resistance exercises
  - "one repetition maximum" test to determine the maximal force
  - same movements against a resistance that was initially set at 50% of the patient's maximal force

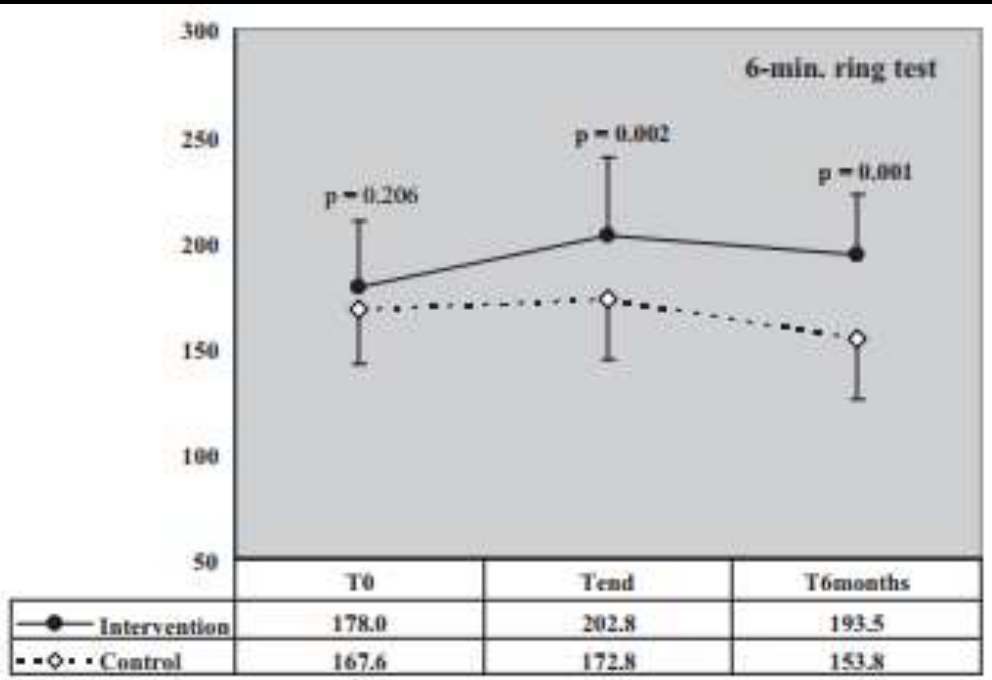
- control group →inpatient PR program that consisted of a minimum of 15 consecutive sessions of specific training for the lower extremities and general exercises

- 6 MRT and ADL field test

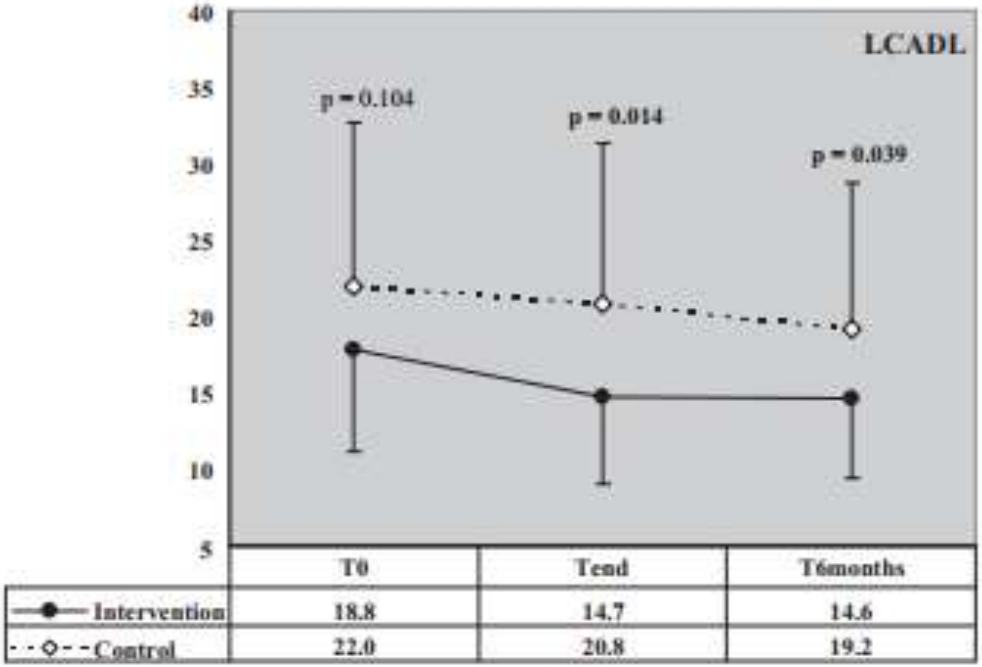
Costi S et al, Chest. 2009;136(2):387

Intervention group

- Improved in the 6MRT and ADL field test compared with those patients in the control group (p = 0.018 and p = 0.010, respectively)
- Reduced perception of fatigue (p<or= 0.006)



	T0	Tend	T6months
Intervention	178.0	202.8	193.5
Control	167.6	172.8	153.8



	T0	Tend	T6months
Intervention	18.8	14.7	14.6
Control	22.0	20.8	19.2

Costi S et al, Chest. 2009;136(2):387

TYPES OF TRAINING

- Continuous vs Interval Exercise
  - Traditionally: continuous, high intensity
  - Similar results with interval training
    - Improved Adherence
- Breathing Retraining
  - Yoga, Pursued Lips, Diaphragmatic breathing
    - Improvement in TLC, dyspnea and saturations
- Others
  - NMES, Tai Chi, Flexibility training, Singing

Education

- Smoking cessation
- LTOT
- Nutrition
- Proper use of medication
- Benefits of exercise and maintaining physical activities

PR Vs Education

- RCT 119 Pts – PR Vs Education
  - greater increase in maximal exercise tolerance (+1.5 METS compared with +0.6 METS [P<0.001]
  - exercise endurance (+10.5 minutes compared with +1.3 minutes [P<0.001])
  - symptoms of perceived breathlessness (score of -1.5 compared with +0.2 [P<0.001]) and
  - muscle fatigue (score of -1.4 compared with -0.2 [P<0.01])
  - self-efficacy for walking (score of +1.4 compared with +0.1 [P<0.05])

Ries AL et al Ann Intern Med. 1995;122(11):823

PR Vs Education

- In another RCT of 119 COPD pts
- 8 wk comprehensive PR programme Vs education
- Randomized to comprehensive group had significant improvement in exercise endurance

- *Only education is not a substitute for exercise training*

Toshima MT, Kaplan RM, Ries AL et al Health Psychol. 1990;9(3):237

Psychological support

- Screening for anxiety and depression should be part of the initial assessment
- Mild or moderate levels of anxiety or depression related to the disease process may improve with pulmonary rehabilitation
- Patients with significant psychiatric disease should be referred for appropriate professional care
  (ATS/ERS STATEMENT)

Exercise – improves depression

- 24 patients with severe COPD showed that pulmonary rehabilitation
  - improved depression scores independent of changes in quality of life and dyspnea

TABLE 2 Depression, anxiety, and dyspnea severity assessed with the Beck Inventory Test and anxiety score assessed with the State Trait Anxiety Inventory in patients randomized to control and pulmonary rehabilitation (experimental group)

	Control Group		Experimental Group	
	Baseline Mean ± SD	After Usual Care Mean ± SD	Baseline Mean ± SD	After PR Mean ± SI
Beck	18 ± 8	16 ± 11	14 ± 8	6 ± 2**
STAI state	19 ± 21	21 ± 21	9 ± 9	8 ± 5
STAI trait	33 ± 25	35 ± 21	35 ± 26	19 ± 8*

STAI, State Trait Anxiety Inventory; PR, pulmonary rehabilitation. * $P = 0.06$; ** $P < 0.01$. PR group compared with baselin using paired t test.

Paz-D´ıaz et al, Am J Phys Med Rehabil 2007;86:30–36

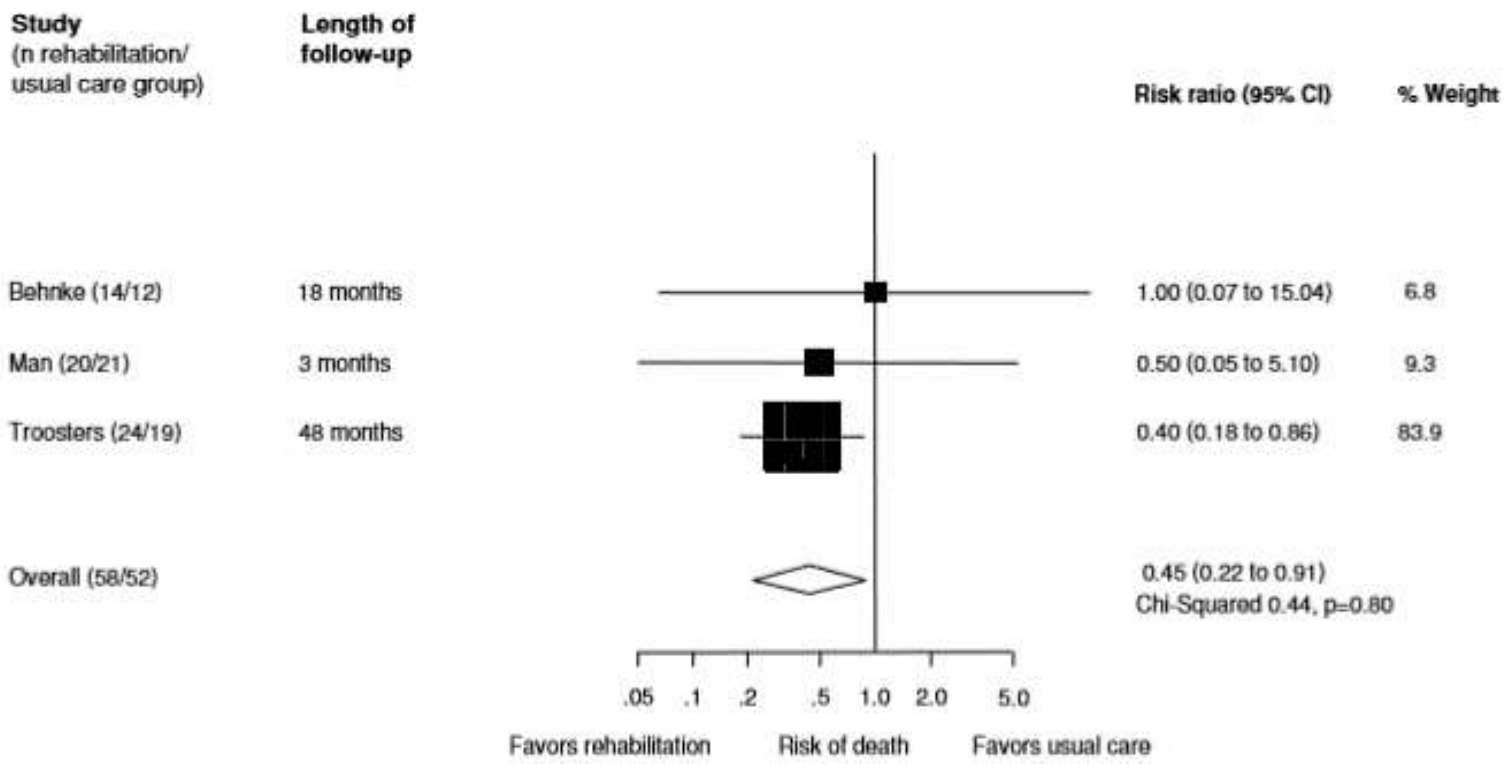
Benefits

Mortality

	Type of study	Patients	Mortality
Ries et al [1]	Prospective observational	1218 (severe)	No difference in mortality
Cote CG et al[2]	Prospective observational	246 pts (mild to severe)	PR Vs no PR → 7% Vs 39% at 2 years

1 - Ries AL et al, Chest. 2005;128(6):3799
2- Cote CG, Celli BR SOEur Respir J. 2005;26(4):630

Mortality



Puhan MA et al Respir Res. 2005;6:54

Exercise capacity & lung function

Ries et al[1]	Prospective observational	1218 pts , Severe emphysema	6 MWT 76 ft
StavD et al[2]	case control	80 pts mod to sev COPD	FEV1 decline (74 Vs 149 ml)
McCarthy et al[3]	Meta analysis	65 RCT	FRC, 6MWT, Max exercise testing improved
Puhan MA et al[4]	Meta analysis	After acute exacerbation	6 MWT (64-215 m)

1 - Ries AL et al, Chest. 2005;128(6):3799
2- Stav D, Raz M et al BMC Pulm Med. 2009;9:26
3- McCarthy B et al Cochrane Database Syst Rev. 2015
4- Puhan MA et al Respir Res. 2005;6:54

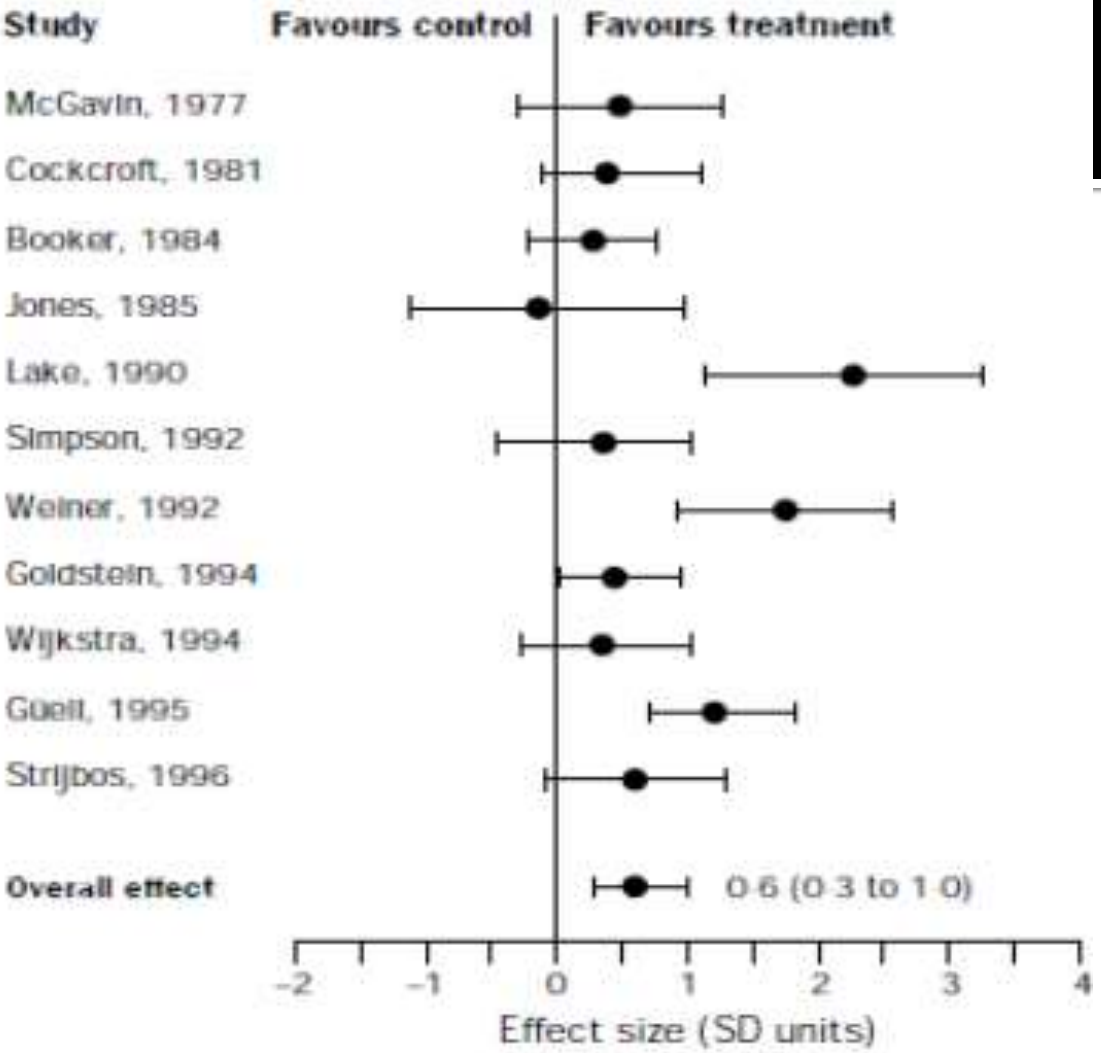


Figure: **Effect of respiratory rehabilitation on functional exercise capacity**

Lacasse,Y et.al. Lancet 1996; 348:1115

Analysis 1.9. Comparison 1 Rehabilitation versus usual care, Outcome 9 Maximal Exercise (Incremental shuttle walk test).

Review: Pulmonary rehabilitation for chronic obstructive pulmonary disease

Comparison: 1 Rehabilitation versus usual care

Outcome: 9 Maximal Exercise (Incremental shuttle walk test)

Study or subgroup	Pulmonary rehab N	Mean(SD)	Usual care N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Casey 2013	148	29 (152)	145	27 (162)		15.2 %	2.00 [-33.99, 37.99]
Deering 2011	11	41.82 (50.56)	14	-1.43 (51.12)		13.1 %	43.25 [3.13, 83.37]
Faulkner 2010	6	-5 (172)	8	12 (125)		1.1 %	-17.00 [-179.62, 145.62]
Griffiths 2000	93	71 (118)	91	-2 (99)		17.9 %	73.00 [41.55, 104.45]
Gurgun 2013	30	56.3 (64.9)	16	8.13 (49.2)		16.6 %	48.17 [14.70, 81.64]
Hernandez 2000	20	9.5 (138.6)	17	-22.9 (167.6)		2.8 %	32.40 [-67.79, 132.59]
McNamara 2013	30	31 (50.7407)	15	-1 (1.81)		29.4 %	32.00 [13.82, 50.18]
Xie 2003	25	70 (138)	25	3 (167)		3.8 %	67.00 [-17.92, 151.92]
Total (95% CI)	**363**		**331**			**100.0 %**	**39.77 [22.38, 57.15]**

Heterogeneity: $Tau^2 = 181.56$; $Chi^2 = 10.34$, df = 7 (P = 0.17); $I^2 = 32\%$

Test for overall effect: Z = 4.48 (P < 0.00001)

Test for subgroup differences: Not applicable

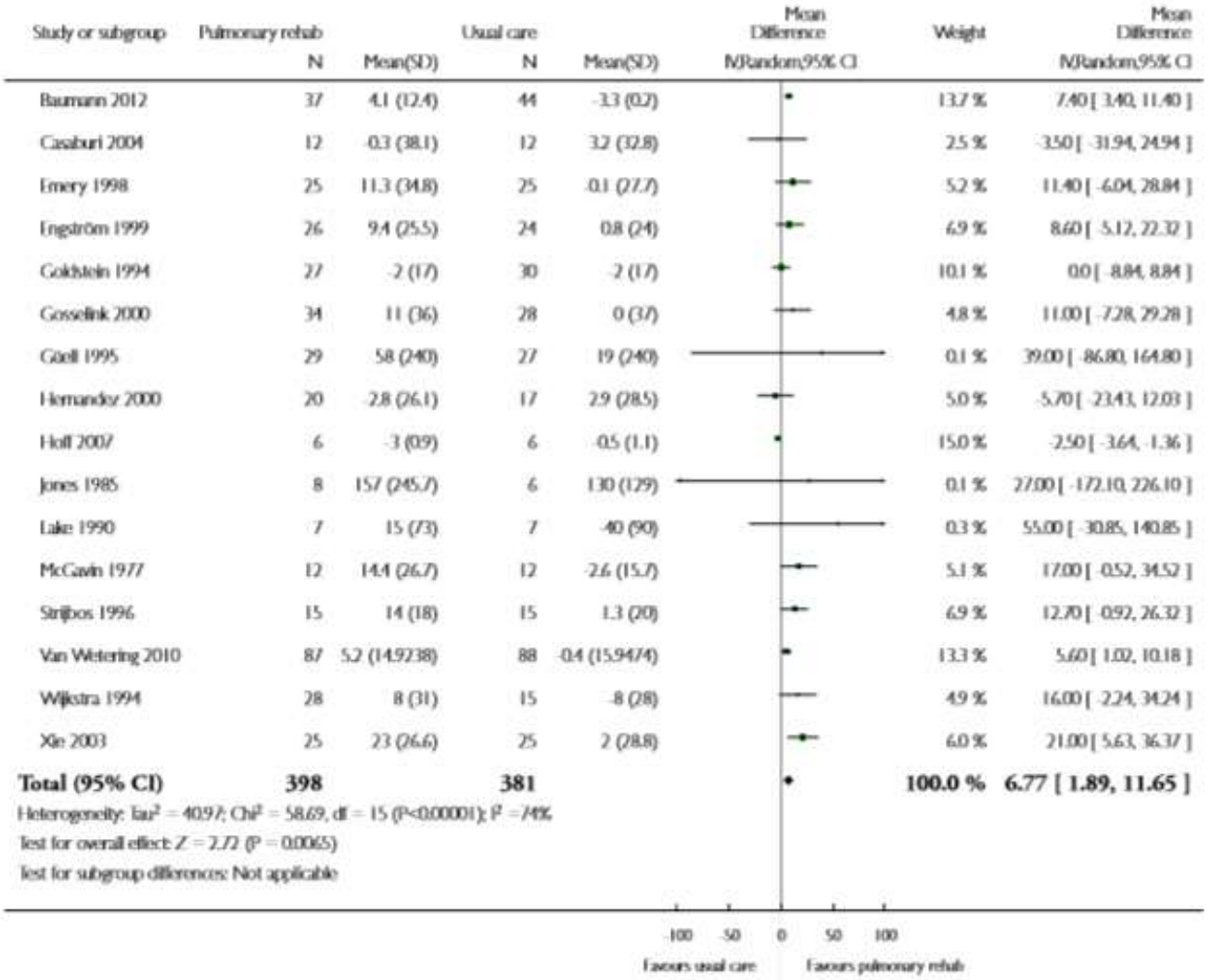
McCarthy B et al Cochrane Database Syst Rev. 2015

Analysis 1.10. Comparison 1 Rehabilitation versus usual care, Outcome 10 Maximal Exercise Capacity (cycle ergometer).

Review: Pulmonary rehabilitation for chronic obstructive pulmonary disease

Comparison: 1 Rehabilitation versus usual care

Outcome: 10 Maximal Exercise Capacity (cycle ergometer)



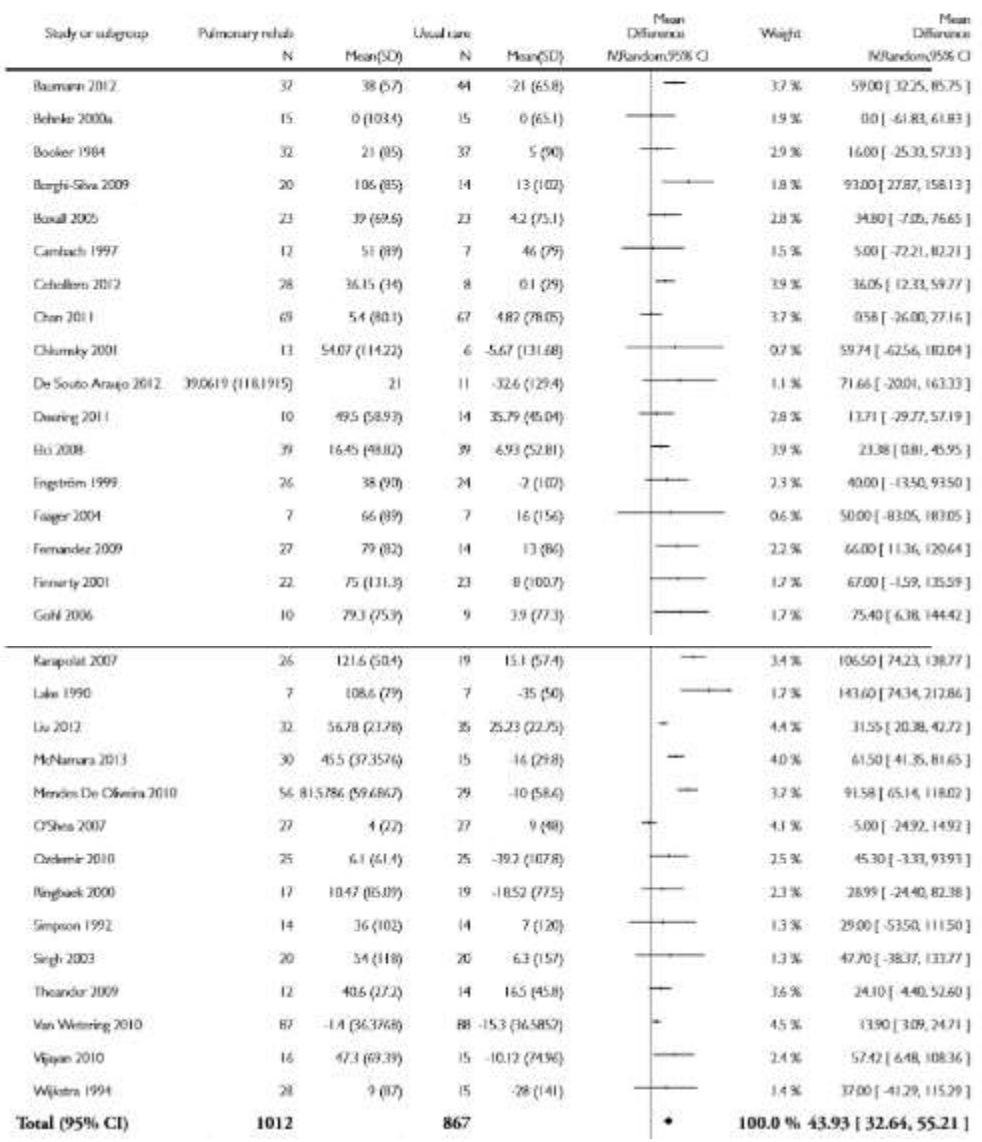
McCarthy B et al Cochrane Database Syst Rev. 2015

Analysis 1.11. Comparison 1 Rehabilitation versus usual care, Outcome 11 Functional Exercise Capacity (6MWT)).

Review: Pulmonary rehabilitation for chronic obstructive pulmonary disease

Comparison: 1 Rehabilitation versus usual care

Outcome: 11 Functional Exercise Capacity (6MWT))



McCarthy B et al Cochrane Database Syst Rev. 2015

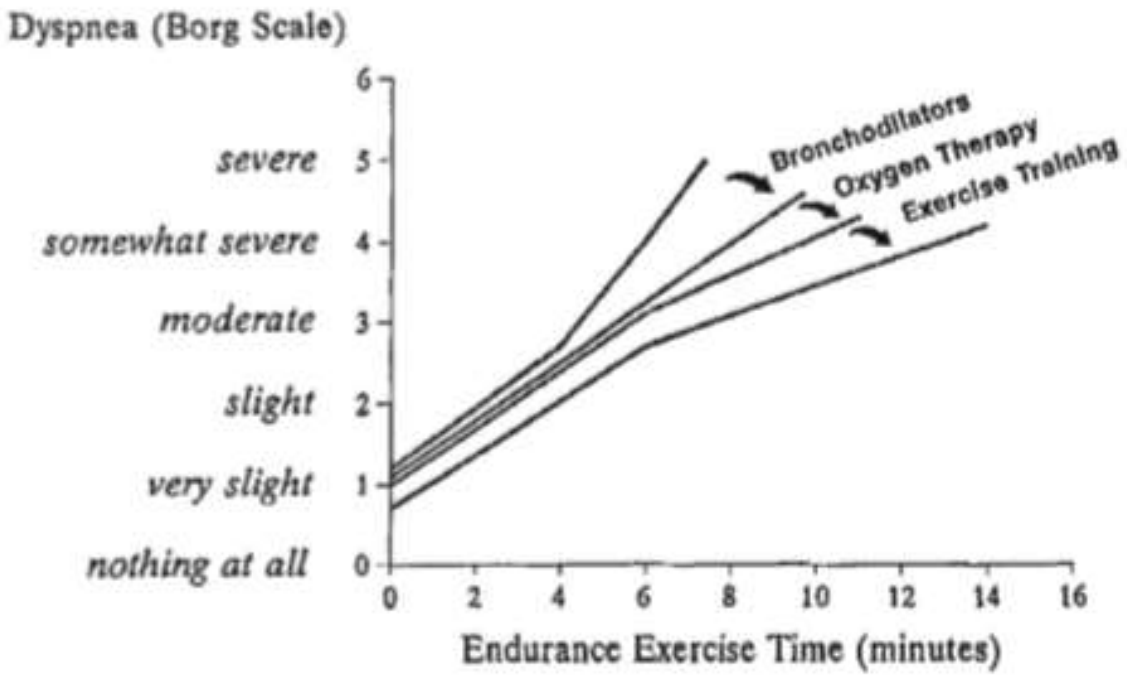


Figure 1. Graphic depiction of a hypothetical case that illustrates the cumulative benefit of interventions targeting pathophysiologic mechanisms of dyspnea.

Am J Respir Crit Care Med 1999; 159;321

Quality Of Life

- Assessed by questionnares (CRQ, SGRQ)
- Dyspnea, fatigue, emotional function improved
- Improvement in both inpatient and outpatient based programmes

Cochrane review – pulm rehab

- In 4 important domains QoL, CRQ scores for dyspnoea, fatigue, emotional function and mastery, the effect was larger than the MCID of 0.5 units
  - Dyspnoea: MD 0.79, 95% confidence interval (CI) 0.56 to 1.03; N = 1283; studies = 19; moderate-quality evidence
  - Fatigue: MD 0.68, 95% CI 0.45 to 0.92; N = 1291; studies = 19; low-quality evidence
  - Emotional function: MD 0.56, 95% CI 0.34 to 0.78; N = 1291; studies = 19
  - Mastery: MD 0.71, 95% CI 0.47 to 0.95; N = 1212; studies = 19; low-quality evidence)

McCarthy B et al Cochrane Database Syst Rev. 2015

Cochrane review – pulm rehab

- Statistically significant improvements were noted in all domains of the St. George's Respiratory Questionnaire (SGRQ)
  - improvement in total score was better than 4 units (MD -6.89, 95% CI -9.26 to -4.52; N = 1146; studies = 19; low-quality evidence)

McCarthy B et al Cochrane Database Syst Rev. 2015

Hospitalization

	Study type	Effect	Result	Comment
Hudson et al[1]	Observational, 44 pts	Decrease in hospitalization	12 days/pt/yr to 5 days/pt/yr	Longest study – 4 yrs
Ries et al [2]	RCT , 119 Pts PR Vs UC	No diff statistically in hospitalization and duration	67% Vs 56% (p 0.32) -2.4 days/pt/yr Vs +1.3 days/pt/yr (P = 0.20)	
Griffiths et al[3]	RCT, 200 Pts PR Vs Uc	No diff in hospitalization, Length of stay was lower	40 Vs 41 pts mean 10.4 [SD 9.7] vs 21.0 [20.7], (p=0.022)	At 1 year

1- Hudson LD et al Chest. 1976;70(5):606
2- Ries et al Ann Intern Med. 1995;122(11):823
3- Griffiths TL et al Lancet. 2000;355(9201):362

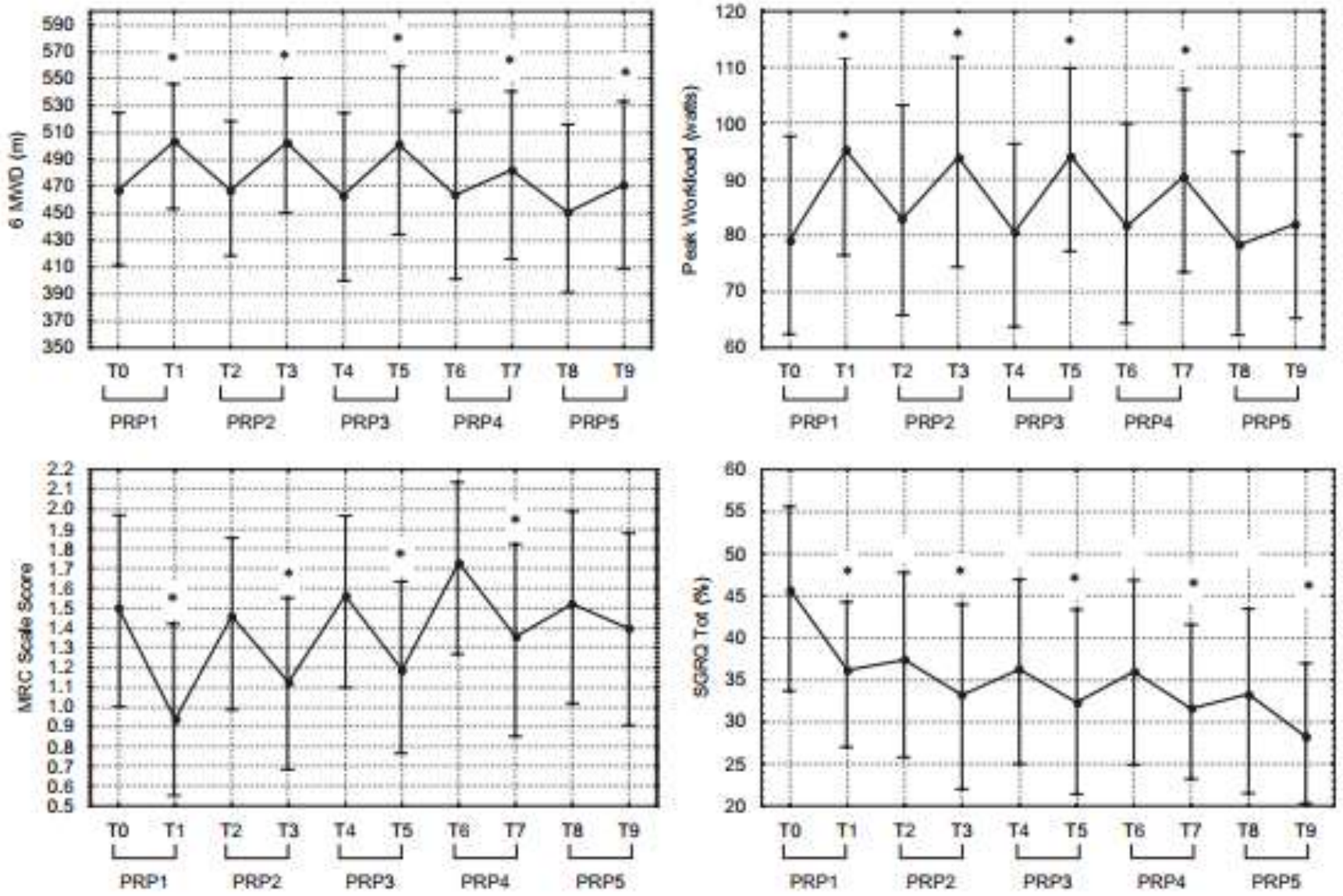
Duration of benefits

- Benefits decline over time

DURATION OF BENEFITS

- 48 patients participating in five successive hospital based PR programs over 7 yrs
  - At the end of each program subjects showed improvement in:
    - Exercise capacity, health status, dyspnea, BODE index
    - Degree of improvement decreased with successive programs
  - Exercise tolerance, Dyspnea, and HRQoL did not worsen despite progressive drop in FEV1
  - FEV1 worsened progressively (mean of 18 ml/yr)

Foglio et al.Respir Med. 2007;101(9):1961



Foglio et al.Respir Med. 2007;101(9):1961

PR – maintenance of benefits

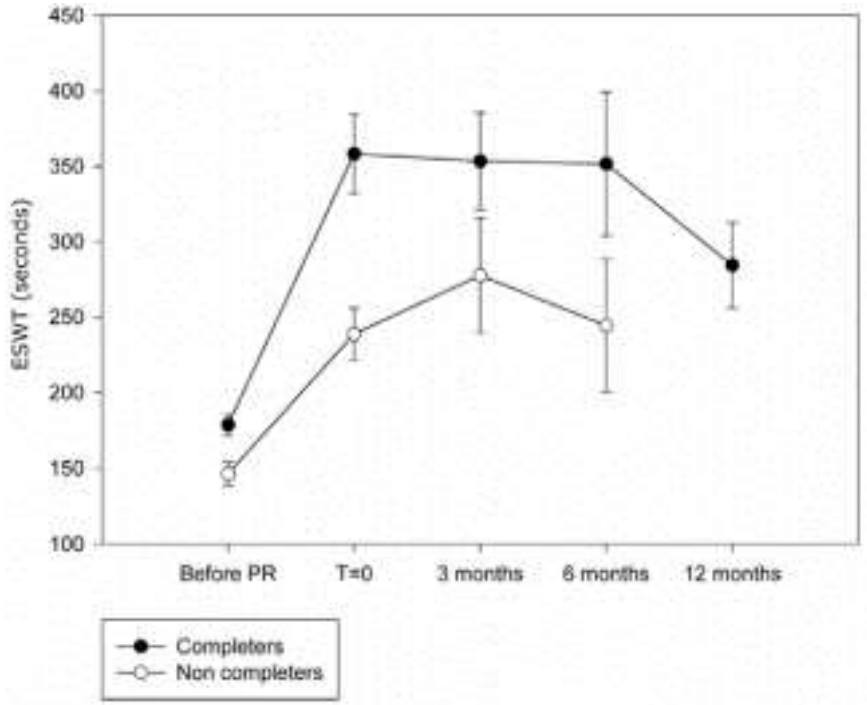
- 209pts of COPD
- 7 wk rehab programme f/b home exercise

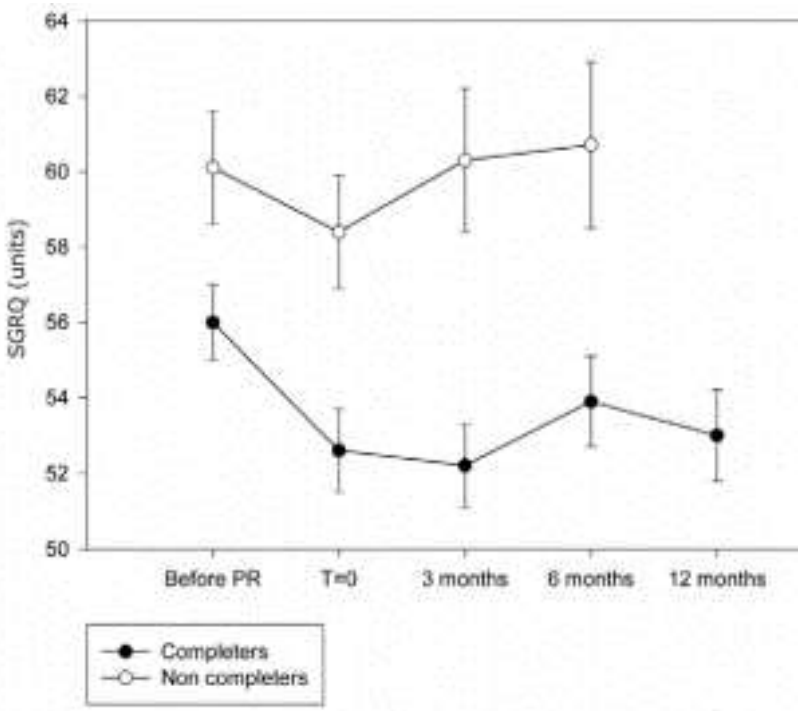
- Maintenance with a simplified program, including self-monitoring, helped to maintain improvements in exercise tolerance and health status

T Ringbaek et al, Chronic Respiratory Disease 2008; 5: 75–80

- Initial improvement after the 7-week program in 141 pts who followed for 1 yr
  - ESWT time was 180 s or 101% ($p = 0.001$)
  - SGRQ 3.4 units ($p = 0.001$)
- These effects were *maintained at the 1-year evaluation*
  - ESWT 59% above baseline; $p < 0.001$
  - Improved SGRQ 3.0 units compared with baseline; $p = 0.011$)
- The 31 patients who attended the 6-month, but not the 12-month evaluation
  - improved ESWT time by 96 s ($p = 0.02$) without any change in SGRQ +2.0 ($p = 0.40$)

T Ringbaek et al, Chronic Respiratory Disease 2008; 5: 75–80





T Ringbaek et al, Chronic Respiratory Disease 2008; 5: 75–80

PR – Duration of Benefits

- Multicenter RCT 143 pts
- After 8 week conventional pulmonary rehabilitation program weekly maintenance program or clinical follow-up for over three years
- Benefits of maintenance were maintained for 2 years, after which the difference between treated and controls waned

	month 0			change month 12-month 0			change month 24-month 0			change month 36-month 0				
Outcome measure	IG (n=65)	CG (n=70)	p value[a]	IG (n=53)	CG (n=50)	p value[b]	IG (n=43)	CG (n=39)	p value[c]	IG (n=34)	CG (n=31)	p value[d]	Time[e]	Group*Time[f]
6MWT	405 ± 111	423 ± 88	0.287	-2.9	-39.3	0.004	-23.3	-48.8	0.046	-32.2	-51.7	0.119	<0.001	0.042
BODE	4.0 ± 1.6	3.7 ± 1.4	0.408	+0.0	+0.3	0.344	+0.3	+0.8	0.043	+0.3	+0.5	0.181	<0.001	0.228
Sf36f	42 ± 15	43 ± 18	0.732	-1.2	-2.3	0.613	-3.8	-2.7	0.783	-0.7	-1.4	0.719	0.142	0.787
Sf36m	57 ± 18	56 ± 2	0.708	-3.0	-1.2	0.312	-6.5	-3.6	0.203	-1.2	-3.0	0.244	0.001	0.478
CRQ Dyspnea	4.8 ± 1.3	4.8 ± 1.4	0.921	-0.4	-0.3	0.468	-0.4	-0.6	0.617	-0.3	-0.7	0.287	0.003	0.294
CRQ fatigue	4.7 ± 1.4	4.6 ± 1.4	0.529	-0.3	-0.2	0.481	-0.6	-0.4	0.380	-0.6	-0.2	0.193	<0.001	0.610
CRQ emotional factor	5.2 ± 1.3	5.0 ± 1.4	0.624	-0.4	-0.4	0.967	-0.5	-0.4	0.734	-0.6	-0.3	0.274	<0.001	0.690
CRQ mastery	5.3 ± 1.5	5.0 ± 1.5	0.244	-0.3	-0.3	0.653	-0.6	-0.1	0.100	-0.4	-0.3	0.894	0.023	0.204

Table III: Full available data analysis of time changes in outcome variables over the 3-year follow-up period (linear mixed models). Values shown at month 0 are m standard deviations. Changes shown between visits are mean changes with respect to month 0 (baseline) values

IG: intervention group; CG: Control group. 6MWT: distance in the 6 minute walking test (meters); SF36f: physical dimension of the short form 36; SF36m: mental dimension of the short form 36; CRQ: Chronic respiratory questionnaire

Güell MR et alAm J Respir Crit Care Med. 2017;195(5):622

LVRS

- NETT
- 1218 pts with emphysema
- 6 to 10 weeks of mandatory pulmonary rehabilitation →randomly assigned to LVRS or continued medical therapy
- LVRS was performed by thoracotomy in 70 % and by VATS in 30 %

NETT trial

- Primary endpoint :
  - mortality
  - maximal exercise capacity at 24 months

LVRS should not be done in …

- FEV_1 of 20 % predicted or less AND either
  - homogeneous emphysema or
  - DLCO that was 20 % predicted or less

- 30-day mortality rate
  - LVRS Vs medical therapy
  - 2.2 % Vs 0.2 % ($p<0.001$)

- At **2 years**

	LVRS	Medical therapy
Mortality (deaths/person year)	0.09	0.10
Improvement in exercise capacity (inc in maximal workload by 10 watts)	16%	3%

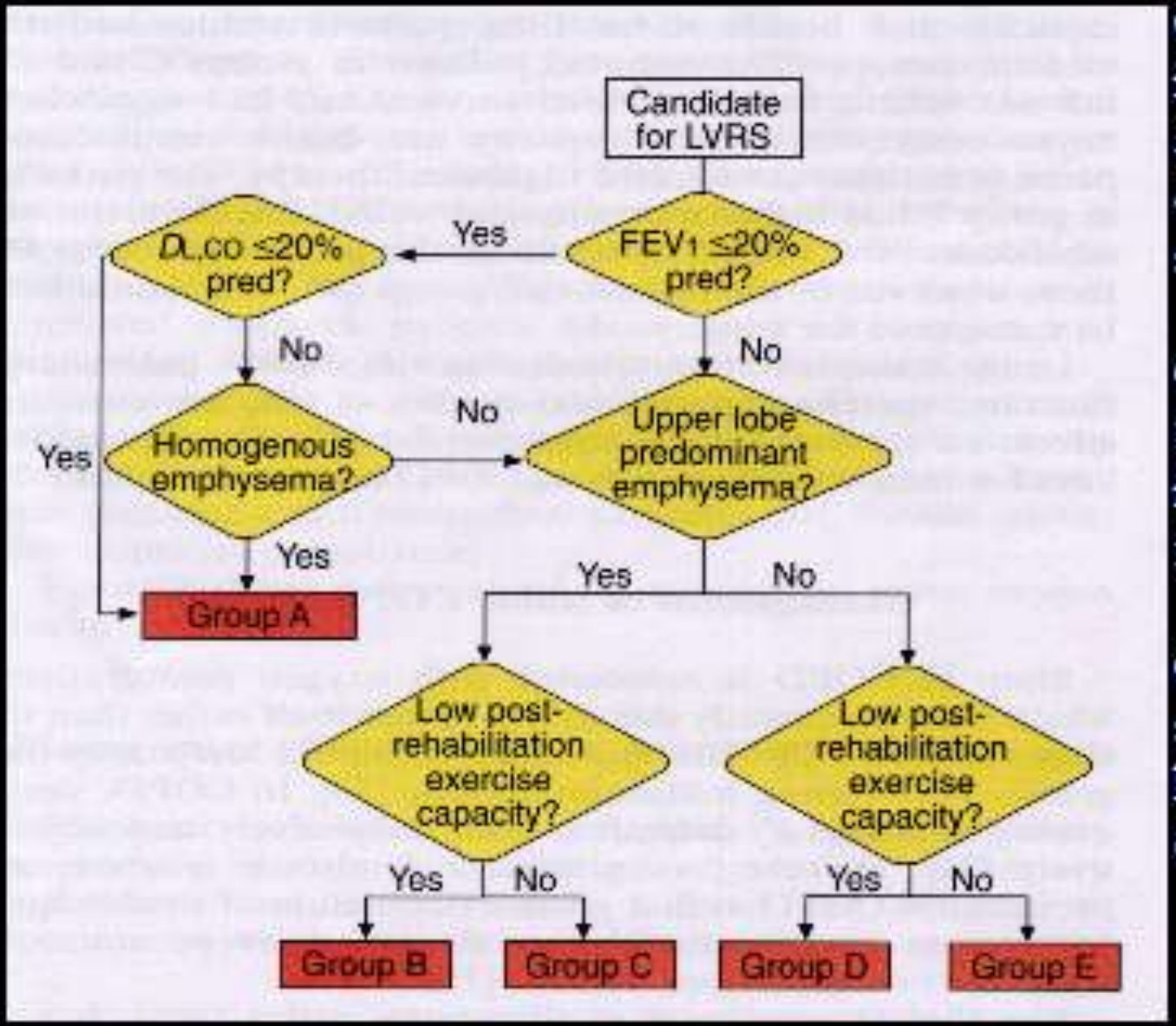
NETT sub group analysis

ients	LVRS	Medical therapy	value	LVRS	Medical therapy	ratio*	P value
ıp A	20/70 (28.6)	0/70 (0)	<0.001	42/70	30/70	1.82	0.06
ıp B	4/139 (2.9)	5/151 (3.3)	1.00	26/139	51/151	0.47	0.005
ıp C	6/206 (2.9)	2/213 (0.9)	0.17	34/206	39/213	0.98	0.7
ıp D	7/84 (8.3)	0/65 (0)	0.02	28/84	26/65	0.81	0.49
ıp E	11/109 (10.1)	1/111 (0.9)	0.003	27/109	14/111	2.06	0.02

ients	Improvement in exercise capacity ¶				Improvement in health-relate quality of life Δ			
	LVRS	Medical therapy	Odds ratio	P-value	LVRS	Medical therapy	Odds ratio	P-val
ıp A	4/58 (7)	1/48 (2)	3.48	0.37	6/58 (10)	0/48 (0)	---	0.03

A- High risk group
B - upper lobe predominant emphysema and a low exercise capacity
C - upper lobe predominant emphysema and high exercise capacity
D - non-upper lobe predominant emphysema and low exercise capacity
E - non-upper lobe emphysema and high exercise capacity

Lung Volume Reduction Surgery, NETT Trial Results
NEJM 2003; 348: 2059-2073



Groups A and E had increased Mortality and should not be considered for surgery.

Group B had increased Survival and symptom improvement following surgery

Group C and D had no survival advantage but had improvement in exercise capacity.

Bronchoscopic LVRS

- Endobronchial placement of one-way valves plugs and blockers
- Endobronchial instillation of biologic sealants
- Thermal airway ablation
- Airway stents for decompression of bullae

Bronchoscopic interventions

REVERSIBLE AIRWAY INTERVENTIONS

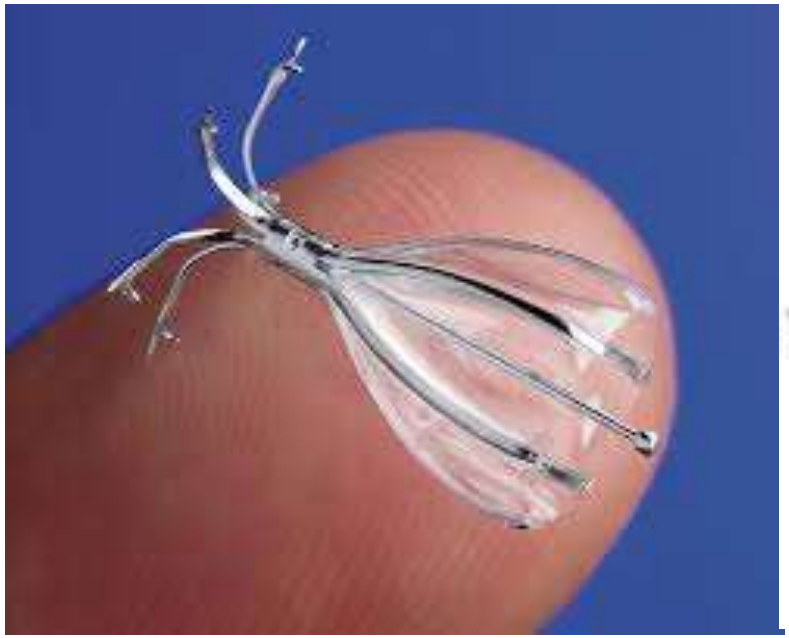
- Endobronchial valves
- LVRCs
- Transbronchial stents

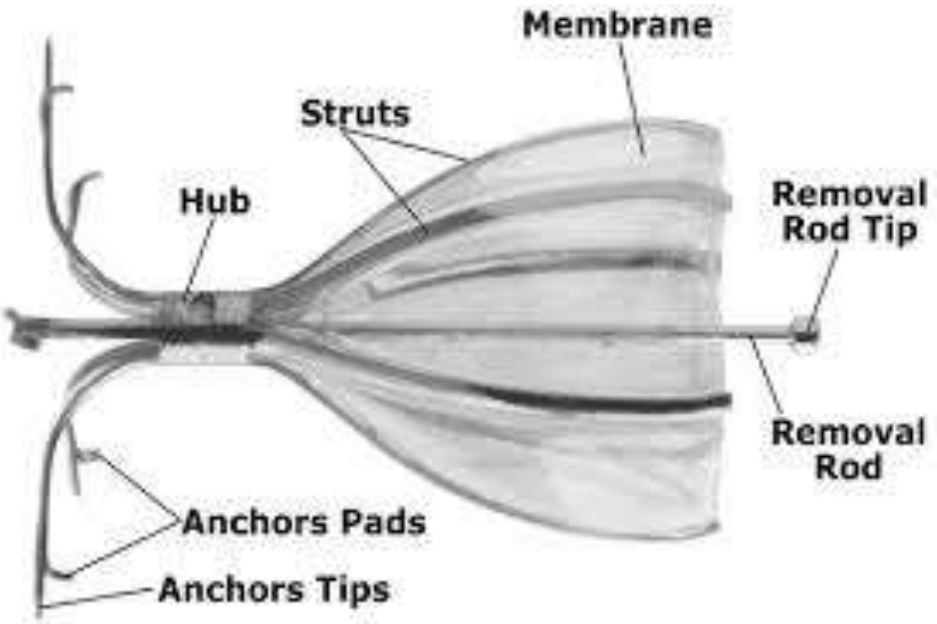
IRREVERSIBLE INTERVENTIONS

- Bronchoscopic thermal vapour ablation (BTVA)
- Biological LVR (BioLVR)

J Thorac Dis 2014;6(11):1640-1653

- Type of Valves-Spiration Inc. and Pulmonx
- Both valves are deployed bronchoscopically and are one-way valves
- Spiration called as "intrabronchial" valve (IBV)
- Pulmonx/Zephyr called as "endobronchial" valve (EBV)
- IBV being similar to an umbrella design and the EBV appearing like a fish mouth facing the proximal airways that springs opens when air or mucus is exhaled from the distal airways but stays closed during all other times

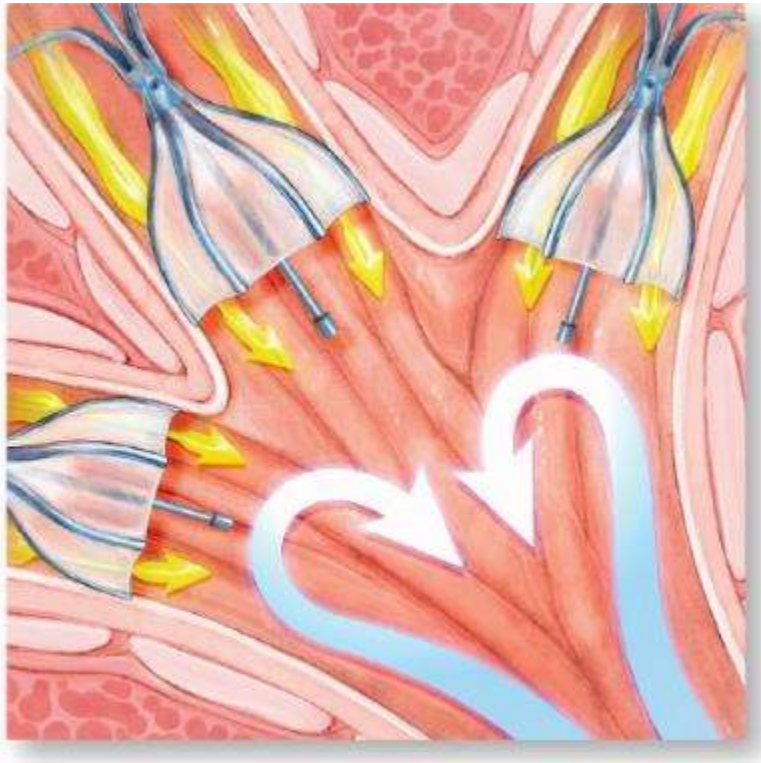



Membrane
Struts
Hub
Removal Rod Tip
Removal Rod
Anchors Pads
Anchors Tips

- IBV(5,6 or 7 mm size) is inserted via the working channel of a flexible bronchoscope on a catheter loader

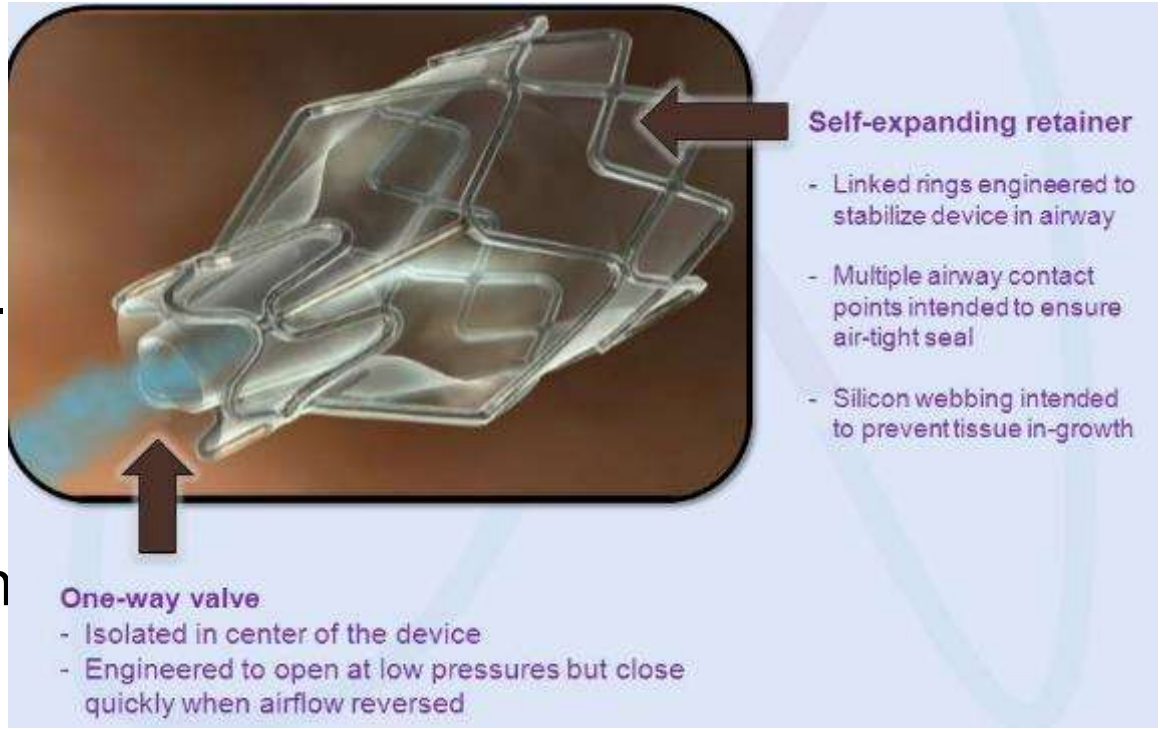
- Once in position valve is deployed so it will sit flush with the carina of the segmental bronchus

- If the valve needs to be repositioned or removed, a standard biopsy forceps is used to grab the central rod; when the rod is pulled, the umbrella collapses and can be removed



ENDOBRONCHIAL VALVES (ZEPHYR)

- Zephyr endobronchial valve (EBV) (Pulmonx) consists of one-way duckbill valve attached to a nitinol (nickel-titanium alloy) self-expanding retaining frame wrapped in a silicone seal



Zephyr valves

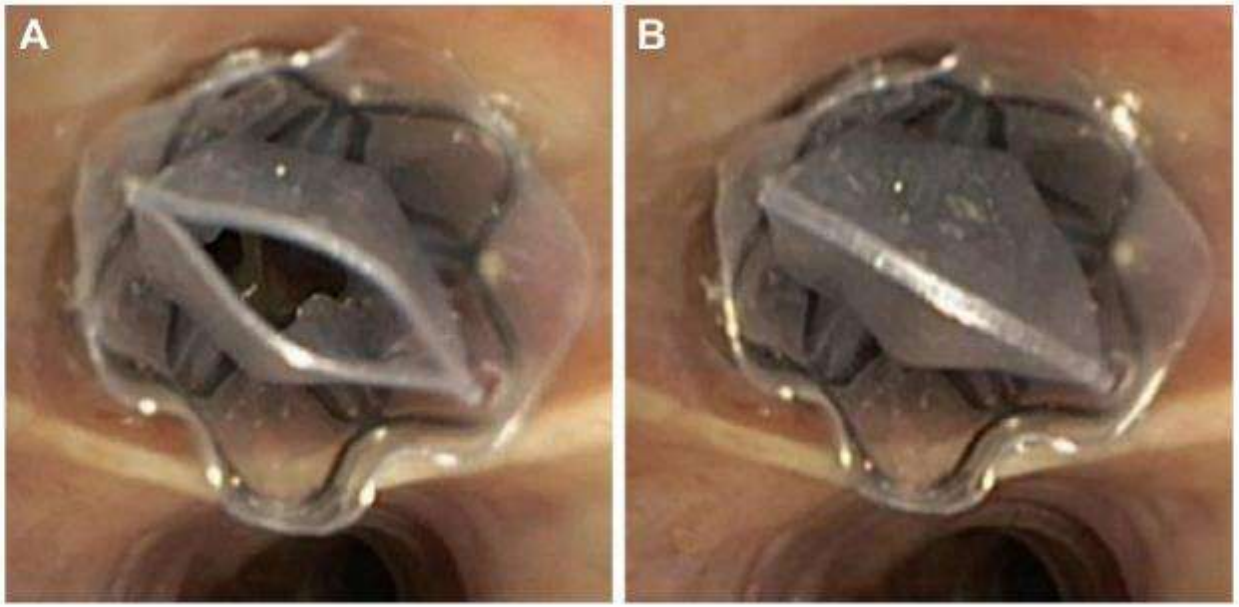


Figure 4 Implanted one-way endobronchial valve.
Notes: (**A**) Open valve, allowing trapped air and fluids to escape. (**B**) Closed valve, no air or fluids can enter the valve.

	Study population	Exclusion criteria	Primary outcome	Targeted lung segment	Complication	Study result	
VENT	heterogenous emphysema FEV1 15-45% TLC>100% Paco2 <50 &Pao2 >45nn of Hg	FEV1 <15%,DLCO< 20%,large bullae, PAH , unstable cardiac condition	Percent change in FEV1 &6MWT at 6 months	Unilateral complete upper lobar occlusio	Death in 2 Pt Hemoptysis (massive) Pneumonia Air leak 6.1% in EBV group &1.2% in control	FEV1 mean 6.8% 6MWt median 5.8% improvement at 6 M	More pronounced in high heterogeneit y group and complete fissure group
STELVIO	severe emphysema (baseline FEV_1 29 ±7 % of predicted) HRCT finding of fissure integrity	Flexible bronchoscopy was performed to determine physiologicall y whether collateral ventilation	Changes from baseline to 6 mnrths in FEV1,FVC & 6MWD	endobronchial valve placement (average four per lobe)	1 death Ptx in 6(18 %)	FEV1 140 ml FVC 347 ml 74 m 6 MWD	More pronounced in high heterogeneit y group

1- Sciurba FC et al Engl J Med. 2010;363(13):1233
2- Klooster K et al N Engl J Med. 2015;373(24):2325

	Study population	Exclusion criteria	Primary outcome	Targeted lung segment	Complication	Study result
IMPACT	homogeneous emphysema with a heterogeneity index between target and adjacent lobes of < 15% FEV1 15-45% TLC>100% Paco2 <50 &Pao2 >45nn of Hg RV>200	Severe bullous emphysema (> 1/3 of the Hemithorax) > 20% difference in perfusion between left and right lung	% change in FEV1 at 3 m	lobe with the highest emphysematous destruction on quantitative analysis by HRCT, the lowest perfusion score, and an absence of CV was chosen as the target lobe	44.2% Vs 12% COPD Exacerbation Ptx(25.6%)	at 3 months improvement in 6 MWT increased by 40 mts(15-65) FEV1 – 17% (8.1-25.8)between group difference

Valipour A et al Am J Respir Crit Care Med. 2016 Nov;194(9):1073-1082

- Degree of lung volume reduction and the associated clinical improvements
  - more in the patients showing complete interlobar fissures on CT and EBV causing complete lobar occlusion
- Complete interlobar fissures suggest absence of collateral ventilation
- Incomplete fissures suggest parenchymal fusion between the lobes and collateral ventilation via channels that bypass the usual airways across the lobes
- Thoracic HRCT scan used to quantify the heterogeneity of emphysema and integrity of interlobar fissure to select the patients potentially eligible for valve treatment

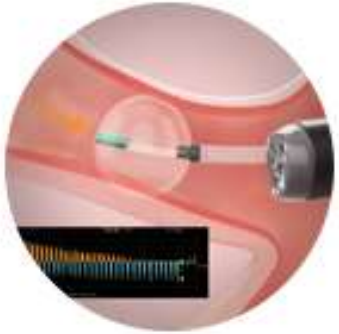
J Thorac Dis 2014;6(11):1640-1653

Chartis System

- The Chartis Pulmonary Assessment System consists of a single patient use catheter with a compliant balloon component at the distal tip, which blocks the airway on inflation
- Air flow out from the target compartment into the environment through the Chartis catheter's central lumen
- By connecting to a console, airway flow and pressure can be displayed
- Airway resistance can be calculated and collateral ventilation in isolated lung compartments can be measured

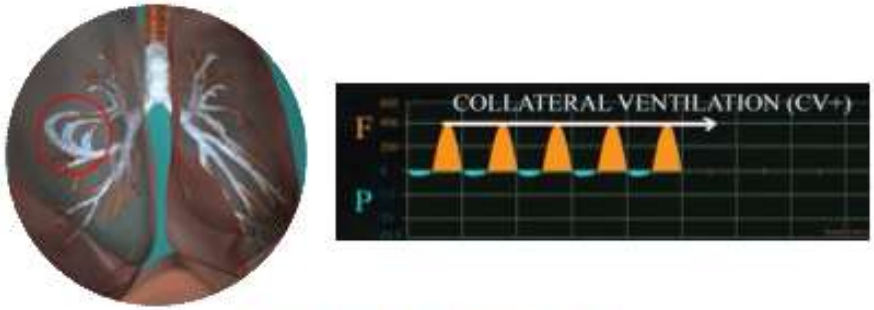
Chartis System

The Chartis balloon catheter is inserted through a bronchoscope to the target airway, and the balloon is inflated to block flow to the target region.



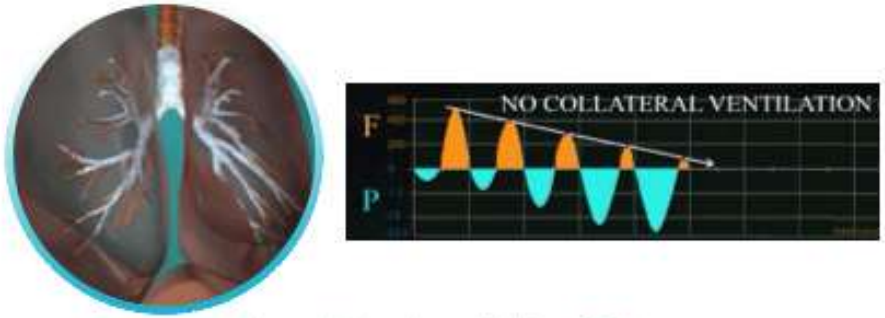
The system calculates airway resistance and measures CV in isolated lobes in the lung. The Chartis console displays expiratory air flow (orange), pressure (blue), and resistance measurements.

Chartis System



Collateral ventilation (CV+)

Expiratory airflow persists over time, indicating the presence of collateral airflow from adjacent lung compartments.



No collateral ventilation (CV-)

Expiratory airflow in the lung compartment is reduced over several breathing cycles, indicating little to no collateral airflow from adjacent lung compartments.

Chartis System

- Herth et al in a prospective multicenter trial of EBV in COPD included 96 patients who underwent the Chartis measurement showed that patients with no evidence of collateral ventilation having median target lobar volume reduction of 55% and a mean 16% FEV1 improvement
- Patients with collateral ventilation had no significant radiological or functional benefits
- Chartis assessment predicted response to valve therapy with 75% accuracy

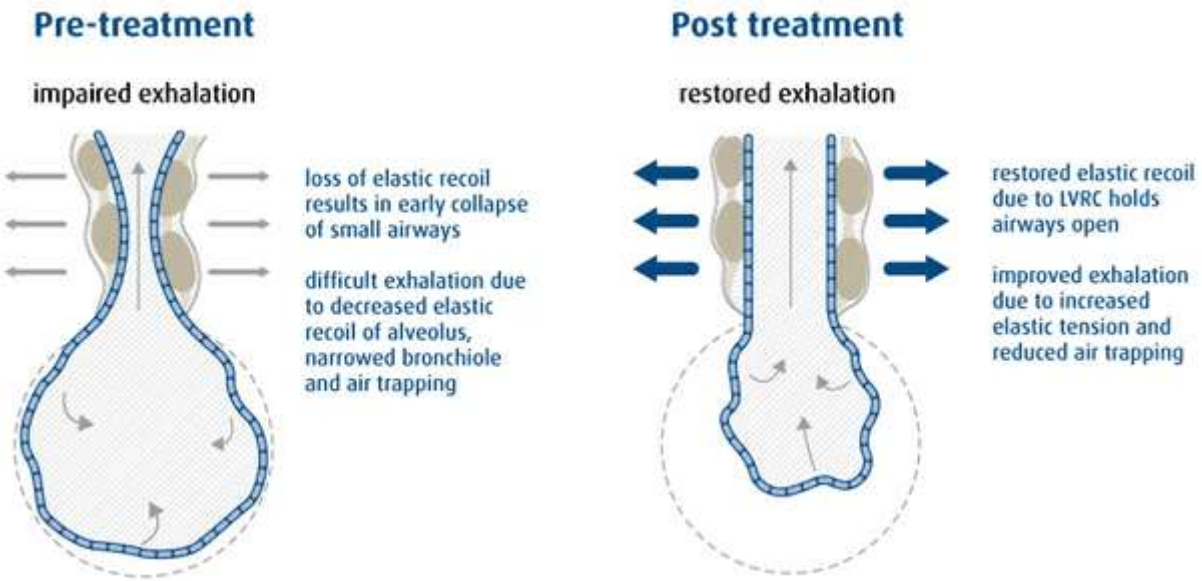
Herth et al Respiration 2010; 79: 5–13

LUNG VOLUME REDUCTION COILS

- The LVR coil is designed to improve the elastic recoil of lung tissue and reduce the airway resistance and hyperinflation in emphysema patients
- Reduction of the residual volume (RV) of the hyperinflated lung improves diaphragmatic function and inspiratory muscle function
- It is effective on heterogeneous and homogeneous emphysema and is independent of collateral ventilation

J Thorac Dis 2014;6(S4):S407-S415

LUNG VOLUME REDUCTION COILS



LUNG VOLUME REDUCTION COILS

- On average, 10–12 coils are placed per upper lobe and 10–14 per lower lobe treatment
- Generally, both sides of the lung are treated, and this is performed in two separate bronchoscopic procedures with 1–2 months in between

Klooster et al. Exp Rev Med Devices 11: 481–489

Endobronchial coils

- Multicenter RCT
- 315 patients
- Predominantly homogeneous emphysema and severe hyperinflation
- Usual care plus B/L placement of endobronchial coils

Sciurba FC et al, JAMA. 2016 May;315(20):2178-89

Endobronchial coils

- Primary effectiveness outcome was
  - absolute change in 6MWT between baseline and 12 months (minimal clinically important difference [MCID], 25 m)
- Secondary end points
  - difference between groups in 6 MWT
  - absolute change in quality of life using SGRQ (MCID, 4)
  - change in forced expiratory volume in the first second (FEV1; MCID, 10%)

Sciurba FC et al, JAMA. 2016 May;315(20):2178-89

Table 2. Effectiveness End Points for the Intention-to-Treat Population[a]

End Point	Coil Treatment (n = 158) At 12 mo	Coil Treatment (n = 158) Within-Group Change or Rate[b]	Usual Care (n = 157) At 12 mo	Usual Care (n = 157) Within-Group Change or Rate[b]	Between-Group Difference for Coil Treatment vs Usual Care (97.5% CI)[b]	P Value[c]
Primary end point						
Change in 6-minute walk distance, median (IQR), m[d]	319.7 (242.9 to 387.7)	10.3 (−33.0 to 45.0)	300.0 (233.2 to 350.0)	−7.6 (−40.0 to 26.0)	14.6 (0.4 to ∞)	.02[e]
Secondary end points						
6-minute walk distance response rate, No. (%) [95% CI][f]	NA	63 (40.0) [31.0 to 49.0]	NA	42 (26.9) [18.9 to 35.0]	11.8 (1.0 to ∞)[g] OR: 1.8 (1.1 to ∞)[h]	.01[i]
Change in FEV_1, median (IQR), %[d]	0.71 (0.58 to 0.88)	3.8 (−6.3 to 16.1)	0.68 (0.54 to 0.82)	−2.5 (−8.9 to 4.4)	7.0 (3.4 to ∞)	<.001[e]
Change in St George's Respiratory Questionnaire score, mean (95% CI)[j]	51.9 (49.5 to 54.4)	−8.1 (−10.2 to −6.0)	58.4 (55.9 to 60.9)	0.8 (−1.2 to 2.9)	−8.9 (−∞ to −6.3)	<.001
Other end points						
St George's Respiratory Questionnaire response rate, No. (%) [95% CI][f]	NA	97 (61.2) [50.9 to 71.4]	NA	43 (27.7) [18.6 to 36.8]	31.6 (20.5 to ∞)[g] OR: 4.1 (2.4 to ∞)[h]	<.001[i]
Change in RV, mean (95% CI), L[j]	4.95 (4.75 to 5.14)	−0.41 (0.57 to −0.25)	5.28 (5.07 to 5.49)	−0.10 (−0.26 to 0.06)	−0.31 (−∞ to −0.11)	.001
Change in RV/TLC, mean (95% CI), %[j]	63.6 (62.4 to 64.8)	−4.0 (−5.1 to −2.9)	67.3 (66.2 to 68.4)	−0.5 (−1.6 to 0.6)	−3.5 (−∞ to −2.1)	<.001

Major complications occurred in 35 % of the coil group
Vs 19 % of the usual care group

Sciurba FC et al, JAMA. 2016 May;315(20):2178-89

Endobronchial coils

- Multicenter RCT in 11 centers
- 60 patients with severe heterogeneous emphysema (mean FEV_1 30.2 percent predicted)
- bronchoscopic placement of nitinol coils (55 b/l & 5 u/l)
- median of 10 coils per lobe

Deslee G et al Thorax. 2014;69(11):980.

Table 5 Responder rates at 6 and 12 months

Variable	MCID	6 months (%)	12 months (%)
FEV_1	≥12%[11]	48.0	40.6
RV	≥0.35[12]	64.8	57.6
6MWD	≥26 m[13]	52.8	60.0
SGRQ	≥4 points[14]	74.1	65.6
SGRQ	≥8 points	61.1	53.1

Pneumonia was the most frequent serious adverse event, occurring in 18 percent of the coil group and 4 percent of the control group

Airway bypass procedure

- Airway bypass or extra anatomic bronchial fenestration
- Decompress areas of emphysema by placing a drug eluting stent through a bronchial wall into an area with severe emphysematous disease

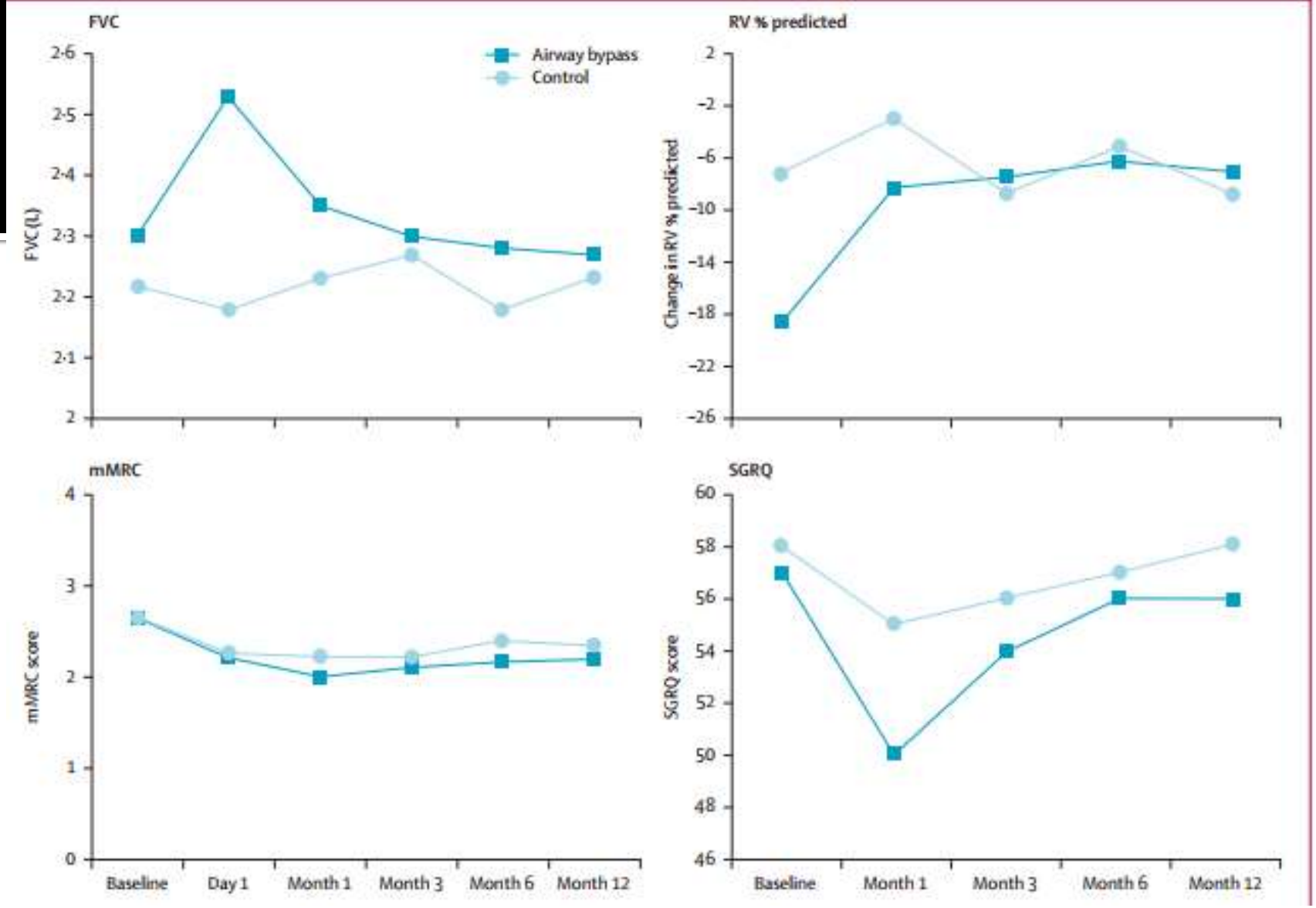
Airway bypass procedure

- Decompression of emphysematous areas
- →decreased trapped gas and hyperinflation
- → chest to resume normal shape and muscle capacity
- → better lung function and decreased dyspnea

EASE TRIAL

- Multicenter RCT of 208 pts
- Homogenous emphysema and with severe hyperinflation -ratio of RV to TLC of ≥0.65
- Primary efficacy endpoint was at least a 12% increase in FVC and at least 1-point decrease in the mMRC dyspnea score from baseline

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



No difference between treatment and sham groups seen in the efficacy or safety endpoints at 6 or 12 months

BIOLOGIC LUNG VOLUME REDUCTION

- Biologic lung volume reduction uses direct application of a sealant/remodeling system to collapse areas of emphysema
- Initial method applied fibrin-thrombin
- Revised technique, called BioLVR, was developed, adding chondroitin sulfate and poly-L-lysine to the fibrin mixture
- An alternative method uses a synthetic polymeric foam sealant called emphysematous lung sealant (ELS)

Biologic lung volume reduction

	No of pts	Biologic	Study popln	
1	22	Hydrogel	Upper lobe rpedominant	6 MWT : no sig change CT at 6 mnths – scarring in high dose group
2	25	Hydrogel 8 subsegemnts	B/L homogenous	significant reduction in gas trapping was observed at 3-month follow-up among HD patients, but not LD patients SGRQ & dyspnea scores better in HD
3	25	ELS	heterogeneous emphysema	Response seen in RV/TLC, FEV1, FVC and SGRQ, mMRC in GOLD III, not in GOLD IV

1- Criner GJ et al Am J Respir Crit Care Med. 2009;179(9):791
2- Refaely Y et al ,Eur Respir J. 2010;36(1):20
3- Herth FJ et al Respiration. 2011;82(1):36

- No phase 3 studies
- Trials are presently to develop reagents with lesser side effect profile

Endoscopic Thermal Vapour Ablation

- Non-blocking technique based on delivering heated water vapour via a disposable bronchoscopic catheter to emphysematous lung parenchyma within a targeted region
- Vapour induces inflammatory reaction & fibrosis resulting in lung volume reduction

Endoscopic Thermal Vapour Ablation

- Thermal energy leads to an inflammatory response causing contraction fibrosis and atelectasis - lung volume reduction
- This remodelled lung tissue does not inflate and reinflate as a result of interlobar collateral ventilation
- No association between efficacy following BTVA and fissure integrity[1]

Gompelmann et al. Respiration 2012;83:400–406

Endoscopic Thermal Vapour Ablation

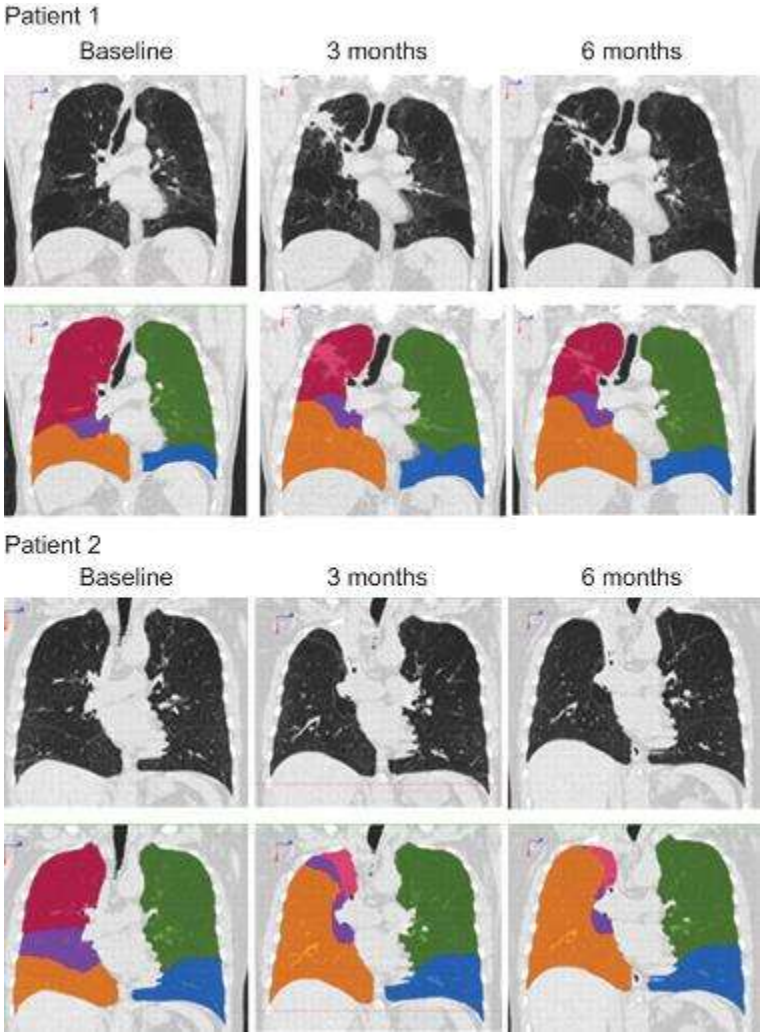
- 44 patients with upper lobe-predominant emphysema were treated unilaterally with BTVA

Endoscopic Thermal Vapour Ablation

- The system consists of a vapour generator, a catheter directed through a flexible bronchoscope
- The procedure plan based on the calculated amount of energy (10 calories/gram of tissue) for each lung segment targeted for treatment
- The amount of tissue determined from software analysis
- Treatment time 3- 10 seconds per airway treated

Snell G et al, European Respiratory Journal 2012 39: 1326-1333

Representative coronal computed tomograms of lungs from two patients before (baseline) and after (3 and 6 months) treatment of right upper lobe using bronchoscopic thermal vapour ablation.



average lobe volume loss from baseline in the treated lobe was 717.6±78.8 mL at 3 months and 715.5±99.4 mL at 6 months ($p<0.001$), which represented a 48% reduction in lobar volume

Gregory Snell et al. Eur Respir J 2012;39:1326-1333

Endoscopic Thermal Vapour Ablation

- At 6 months,
  - mean±SE FEV_1 improved by 141±26 mL (p<0.001)
  - residual volume was reduced by 406±113 mL (p<0.0001)
  - SGRQ total score improved by 14.0±2.4 points (p<0.001) with 73% improving by ≥4 points
  - 6MWD improved by(46.5±10.6 m) (p<0.001)
  - mMRC dyspnoea score (0.9±0.2) (p<0.001)

Gregory Snell et al. Eur Respir J 2012;39:1326-1333

- Unilateral lobar Inter Vapor treatment of heterogeneous emphysema improved lung function and health outcomes

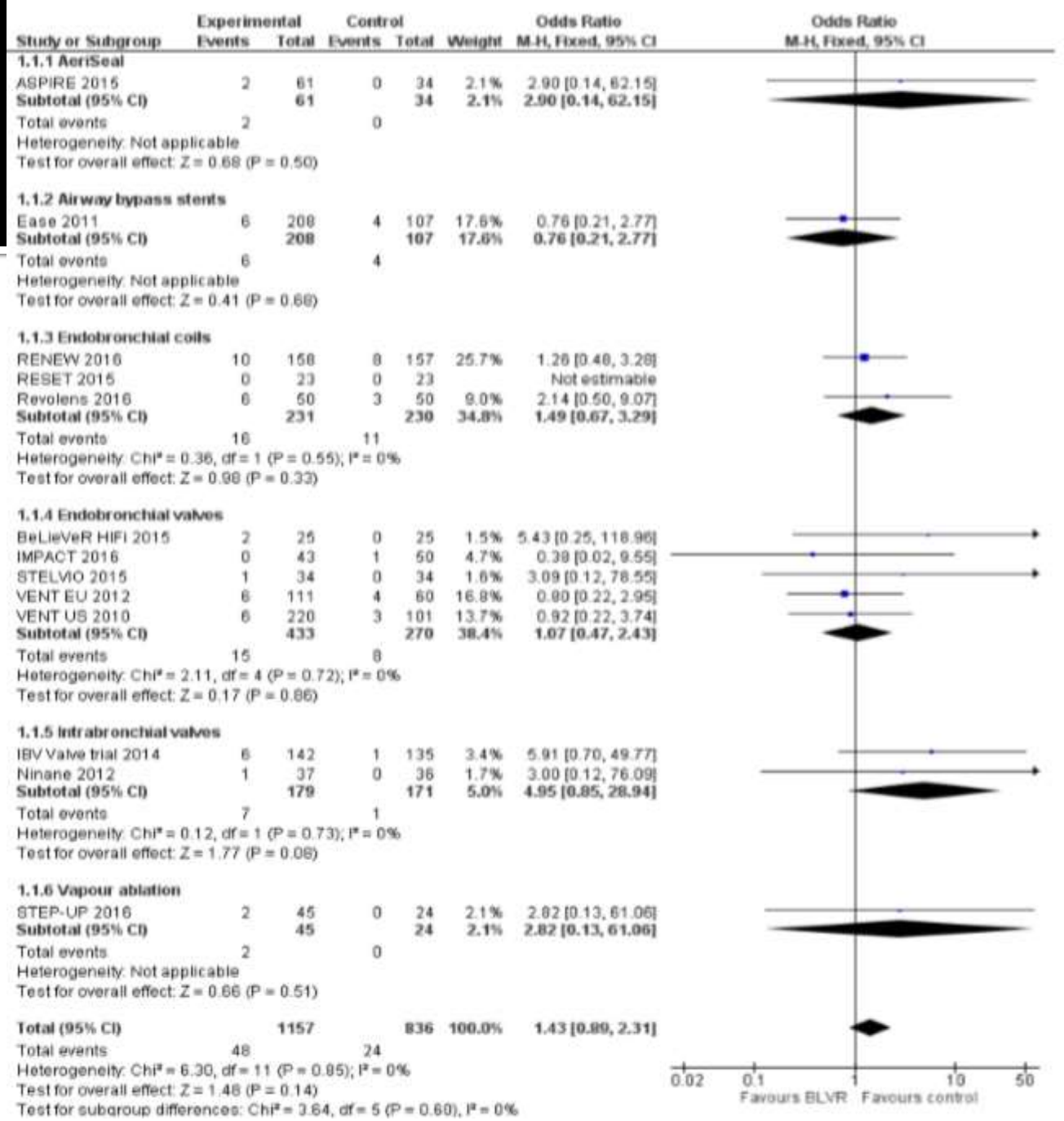


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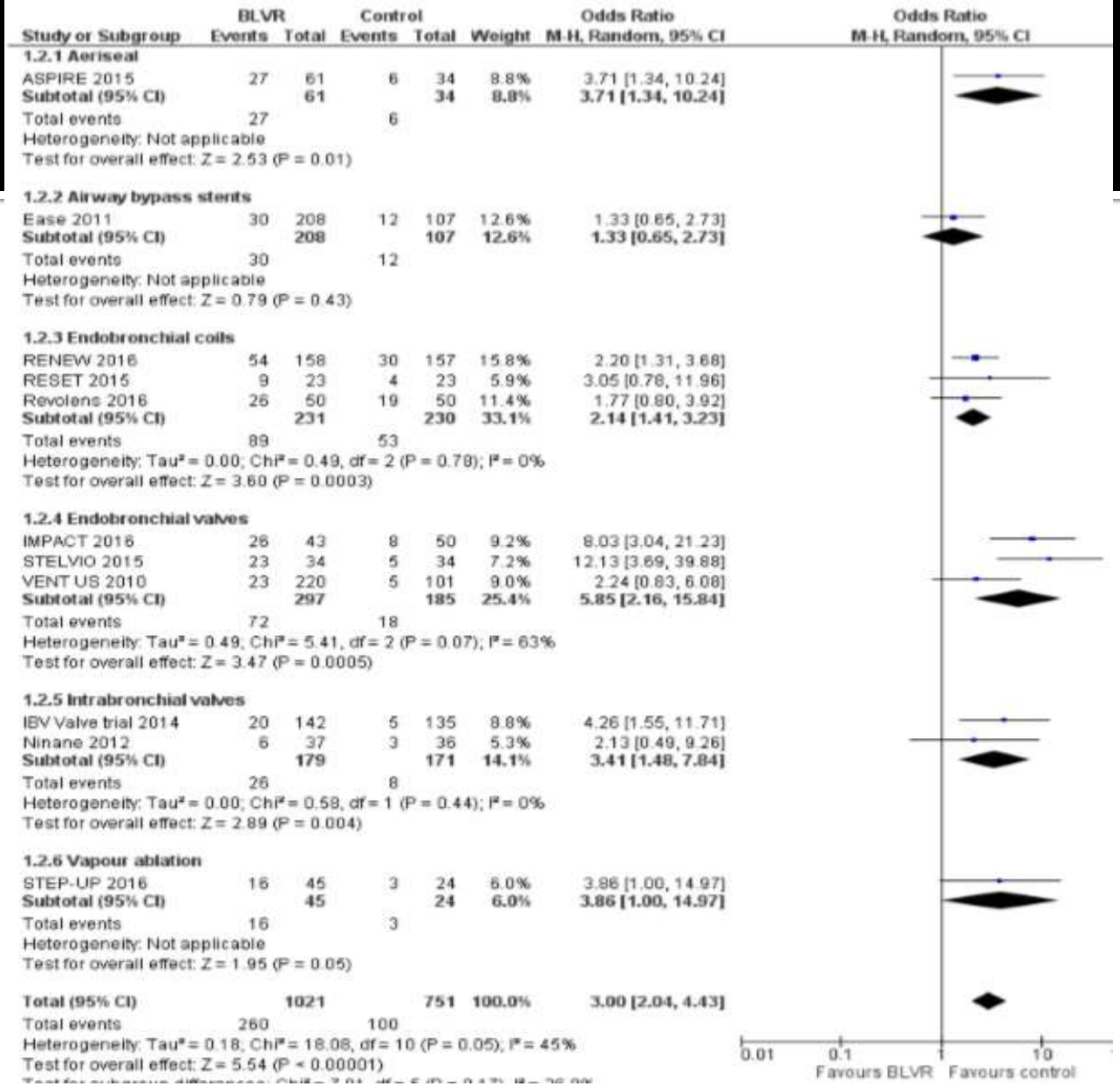
Figure 5. Forest plot of comparison: 1 BLVR to medical therapy, outcome: 1.2 Adverse Events (all met end of follow-up).



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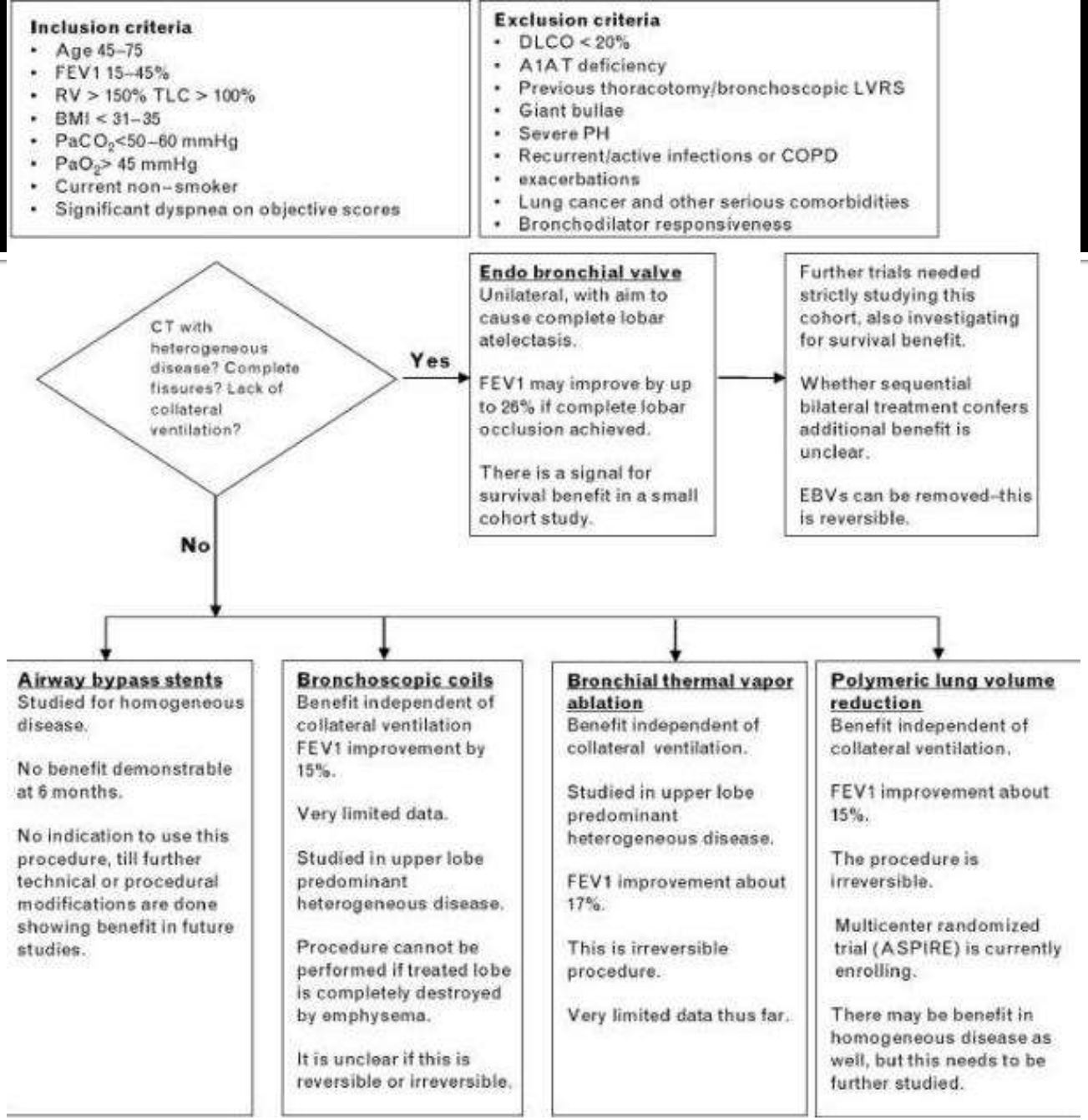


Curr Opin Pulm Med. 2013;19(2):145-151

Vaccinations

- Pnuemococcal vaccine
- Influenza vaccine

Vaccination

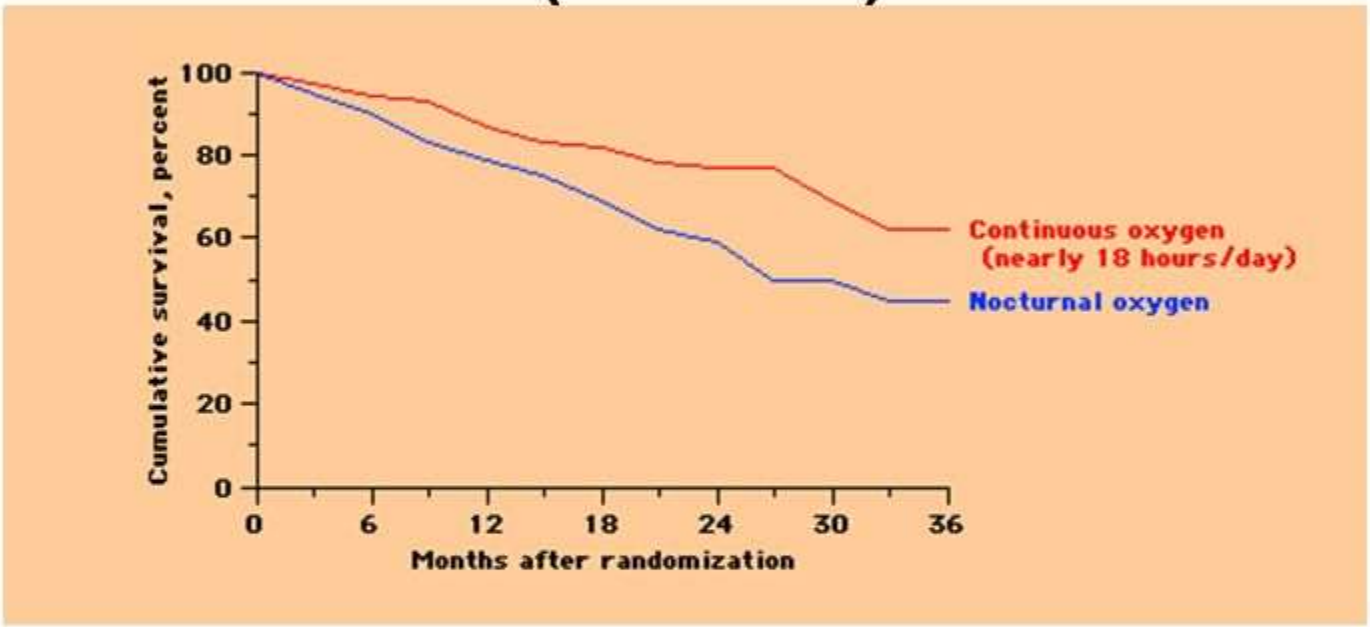
- Infections → COPD exacerbations
- Vaccinations reduce incidence of infections
- Cochrane review of 2469 pts in 6 trials[1]
  - Significant reduction in the total no of exacerbations
  - weighted mean difference (WMD) -0.37, 95% CI -0.64 to -0.11, P = 0.006
- RCT of 125 pts[2]
  - Vaccination reduced influenza by 76 %

1- Poole PJ et al Cochrane Database Syst Rev. 2006 Jan 25;(1):CD002733
2- Wongsurakiat P et al Chest. 2004;125(6):2011

Oxygen therapy

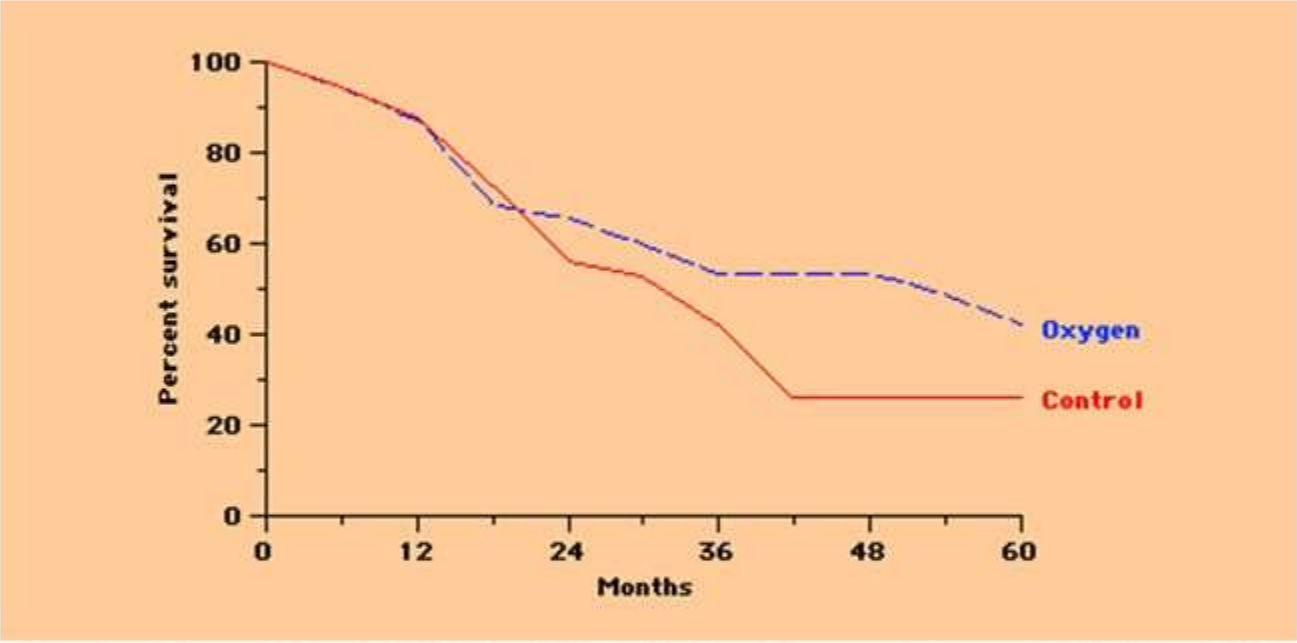
- Evidence:
  - Nocturnal Oxygen Therapy Trial (NOTT)
  - Medical Research Council (MRC) study
    - Relationship between survival and the average daily duration of oxygen use
    - Median survival in those using O2 for 18 hours/day was approximately two-fold longer than in those receiving no O2
    - Survival curves for O2 treated subjects in subsequent uncontrolled studies have generally produced results that are consistent with the data from similarly treated groups of the NOTT and MRC studies

Survival with LTOT in COPD Nocturnal Oxygen Therapy Trial (NOTT)



Survival benefit of continuous long-term oxygen therapy in COPD The Nocturnal Oxygen Therapy Trial randomly assigned 203 patients with chronic obstructive pulmonary disease complicated by hypoxemia to treatment with nearly continuous oxygen therapy (red line) or nocturnal oxygen alone (blue line). Continuous oxygen therapy was associated with a significant survival benefit ($p = 0.01$). (Redrawn from Nocturnal Oxygen Trial Therapy Group, Ann Intern Med 1980; 93:391.)

LTOT in COPD
Medical Research Council (MRC)



Survival benefit of LTOT in COPD Medical Research Council Trial in which 87 patients with chronic obstructive pulmonary disease, severe hypoxemia, hypercapnia, and a history of congestive heart failure were randomized to treatment with oxygen therapy for at least 15 h/day (blue dashed line) or no oxygen (red line). Continuous oxygen therapy led to a significant survival benefit. (Report of the Medical Research Council Working Party, Lancet 1981; 1:681.)

LTOT WITH EXERCISE & moderate deaturation – LOTT

- No mortality benefit
- No difference in hospitalization
- No changes in measures of
  - Quality of life
  - Depression
  - Anxiety
  - Functional status

The Long-Term Oxygen Treatment Trial Research Group N Engl J Med 2016; 375:1617-1627

LTOT

- Stable disease on a full medical regimen
  - PaO_2 < 55 mmHg (corresponding to an SaO_2 <88%)
  - PaO_2 is 55-59 mmHg (SaO_2 89%) and who exhibits signs of tissue hypoxia:
    - pulmonary hypertension
    - cor pulmonale
    - erythrocytosis
    - edema from right heart failure

AJRCCM

- Double Blinded Trial
- 29 non-hypoxic patients with COPD (FEV1 36%)
- Cycle Egrometers, 45min, 3/wk, 7wks
- During exercise 3 L/min oxygen vs compressed air

LTOT – GREY AREAS

- Patient with adequate PaO_2 who have severe dyspnea relieved by low-flow oxygen
- Patients who are limited in their exertional capacity but improve their exercise performance with supplemental oxygen

NOCTURNAL NIPPV

- Uncontrolled Trials
- Benefits:
  - Dyspnea
  - Improvement of Hypersomnolence
  - Daytime CO_2
- Variable compliance complicates interpretation

NOCTURNAL NIPPV

- Cochrane Airways Group 7 RCT (245 pts)
  - 3 and 12 month follow-up
  - No significant difference:
    - $PaCO_2$ (2.5 mmHg) or PaO_2
    - 6 min walk distance
    - Health related QOL
    - FEV1/FVC, Max Inspiratory Pressures
  - Subgroups with benefit at 3 months
    - IPAP > 18cmH20
    - Used NIPPV > 5 hrs nightly
    - Baseline $PaCO_2$ > 55 mmHg

NOCTURNAL NIPPV

- Survival
  - AVCAL Study
    - 145 pts controlled trial, LTOT vs LTOT/NPPV
    - Mean f/u 2.2yrs, compliance 4.5 hrs/night
    - Improved survival out to 36 months, beyond which survival curves converged
- Hospitalization
  - Italian MCT, 122 Stable COPD (LTOT vs LTOT/NPPV)
  - After 2 yrs, no difference in Mortality or Hospital Admissions

NUTRITION AND COPD

- Adequate calories to meet or slightly exceed their basal energy expenditure
  - Consultation with a registered dietician to develop a nutritional prescription for food intake is often helpful
- Small, frequent meals
- Meals requiring little preparation (eg, microwaveable, liquid supplements)
- Rest before meal

NUTRITION AND COPD

- Barriers:
  - Fatigue and dyspnea (interfere with food preparation and consumption)
  - Chronic sputum production (alters the taste of food)
  - Flattening of the diaphragm (causes early satiety)
  - Depression
  - Side effects of medications (eg, nausea, indigestion)

Lung transplantation

- The following are suggested criteria for placing a patient with COPD on the transplant list (presence of one criterion is sufficient)
  - BODE index ≥7 (calculator 3)
  - FEV1 <15 to 20 percent of predicted
  - ≥3 severe exacerbations in the preceding year
  - One severe exacerbation with acute hypercapnic respiratory failure
  - Moderate to severe pulmonary hypertension

Weill D et al, J Heart Lung Transplant. 2015;34(1):1

Take Home Message

- All symptomatic COPD pts should be considered for pulmonary rehabilitation
- Pulm rehabilitation to be followed at home
- LVRS - upper lobe predominant with low exercise capacity
- bLVRS- future for COPD patients failing optimal medical therapy