How to Utilize Oxygen in Pulmonary Rehabilitation?

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Contents

- Introduction of guideline of oxygen therapy and key landmark studies on long-term oxygen therapy
- Ambulatory oxygen therapy and recent studies on oxygen supply in pulmonary rehabilitation
- Current situation about ambulatory Oxygen
- Summary

Terminology for Home Oxygen Therapy

Term	Definition
Ambulatory oxygen	Oxygen delivered during exercise or activities of daily living.
Continuous-flow oxygen	Oxygen delivered at a constant flow rate, regardless of the respiratory rate, in contrast to pulse-dose oxygen (*see below*).
Continuous oxygen	Oxygen prescribed 24 h/d.
Home oxygen	Oxygen delivered in a home, also known as domiciliary oxygen. It includes not only long-term oxygen but also short-term, nocturnal, palliative, ambulatory, and short-burst oxygen. It excludes oxygen use in healthcare and emergency settings.
Long-term oxygen	Oxygen that is delivered to patients with chronic hypoxemia, in most cases for the remainder of the patient's life. Long-term oxygen therapy is prescribed for at least 15 h/d.
Nocturnal oxygen	Oxygen delivered during sleep time only.
Palliative oxygen	Oxygen to relieve dyspnea. Palliative oxygen may be provided continuously, nocturnally, or during ambulation. Short-burst oxygen therapy falls into this category.
Portable oxygen	Oxygen delivered through systems that are sufficiently lightweight so that they can be carried or pulled by patients and allow them to leave their home (e.g., oxygen cylinders or canisters carried or pulled in trolleys or portable oxygen concentrators).
Pulse-dose oxygen	Oxygen delivered during inspiration only in such a way that the quantity of oxygen administered is influenced by the respiratory rate. The delivery system is at rest while the patient is exhaling.
Short-burst oxygen	Brief and intermittent oxygen administration before and/or after exercise, generally used as needed, in the absence of known hypoxemia.
Short-term oxygen therapy	Oxygen provided temporarily, during a period of severe hypoxemia (e.g., during the course of and shortly after an exacerbation of COPD).

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.
There are several types of home oxygen therapy. This table is provided to assist in standardizing the terminology and is adapted by permission from Reference 22.

Am J Respir Crit Care Med 202;202:e121-e141

Guidelines for oxygen therapy

	ATS (2020)	BTS (2015)	TSANZ (2016)	German (2008)
LTOT	o	o	o	o
AOT	o	o	o	o
NOT		o	o	o
Palliative OT		o	o	
Short burst OT		o		

Am J Respir Crit Care Med 202;202:e121-e141
. Thorax 2015;70:i1–i43
Respirology 2016;21:76-78
Respiration 2017;93:253–263

Primary diagnosis for starting LTOT

- LTOT registry of Sweden (n=23,909)

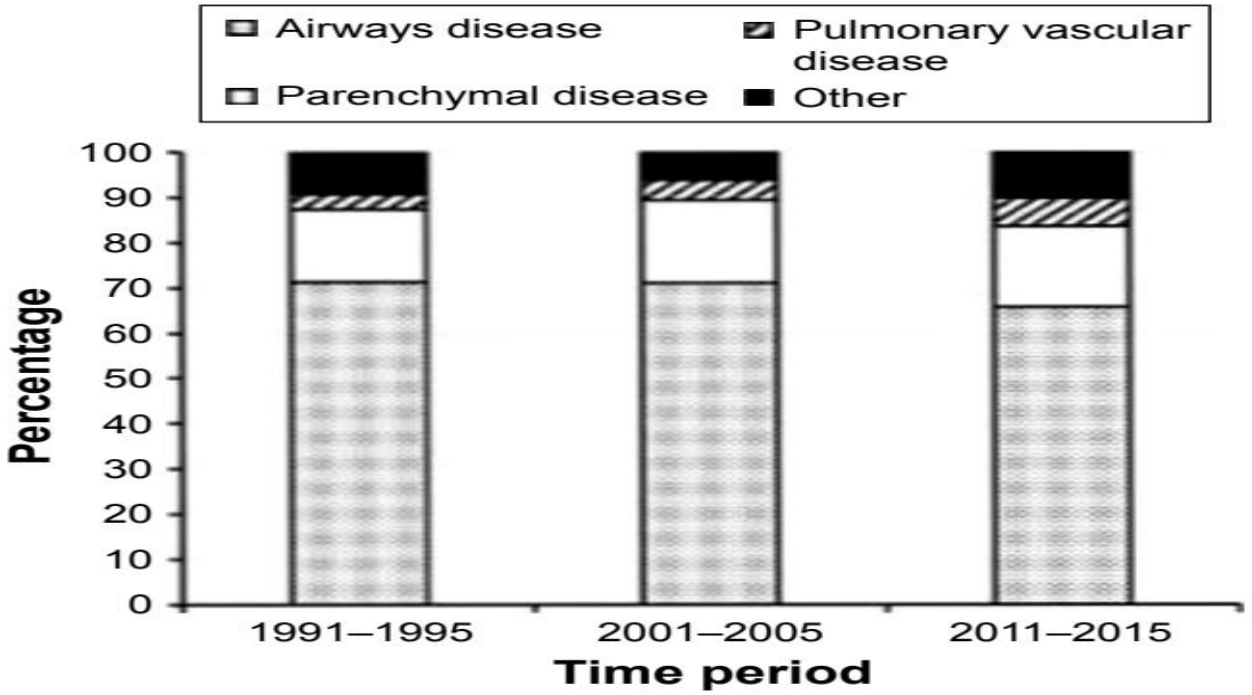

Figure 1 Primary physician-diagnosed cause for starting LTOT.
Notes: Reasons for starting LTOT: airways disease, parenchymal disease, pulmonary vascular disease, and other. Airways disease was the main underlying cause for prescribing LTOT (69%).
Abbreviation: LTOT, long-term oxygen therapy.

Airways disease was the main underlying cause for prescribing LTOT (n=15,840; 69%) with 14,420 (62%) patients having physician-diagnosed COPD.

Long-term oxygen therapy (LTOT)

- Established as the standard of care for selected patients with advanced chronic stable hypoxemia

- Two landmark randomised studies
  - Nocturnal Oxygen Treatment Trial
  - Medical Research Council study
    - ☞ Improving Survival in COPD with severe resting hypoxemia

- *less hypoxaemic patient*
- *isolated nocturnal hypoxaemia*

NOTT and MRC

Table 2
Study populations and key findings of the NOTT and MRC trials

	NOTT[11]	MRC[14]
Inclusion criteria	• Pa_{O_2} ≤55 mm Hg (≤7.3 kPa), or • Pa_{O_2} ≤59 mm Hg (≤7.87 kPa) accompanied by either edema, P-pulmonale (electrocardiogram) or raised hematocrit (≥55%)	• Pa_{O_2} 40–60 mm Hg (5.3–8 kPa) and at least 1 recorded episode of heart failure with ankle edema
Results	The 24-mo mortality rate was significantly lower in patients randomized to continuous oxygen therapy (mean usage ~18 h/d) than in those randomized to 12 h/d of nocturnal oxygen therapy (22.4% vs 40.8%, respectively; $P<.01$)	The 5-y mortality rate was significantly lower in the LTOT group (usage ≥15 h/d) than in control subjects who did not receive LTOT (risk of death 12%/y vs 29%/y, respectively; $P = .04$)

Abbreviations: LTOT, long-term oxygen therapy; MRC, Medical Research Council long-term domiciliary oxygen therapy trial; NOTT, nocturnal oxygen therapy trial; Pa_{O_2}, arterial partial pressure of oxygen.

Data from Refs.[11,14]

NOTT trial

All Subjects

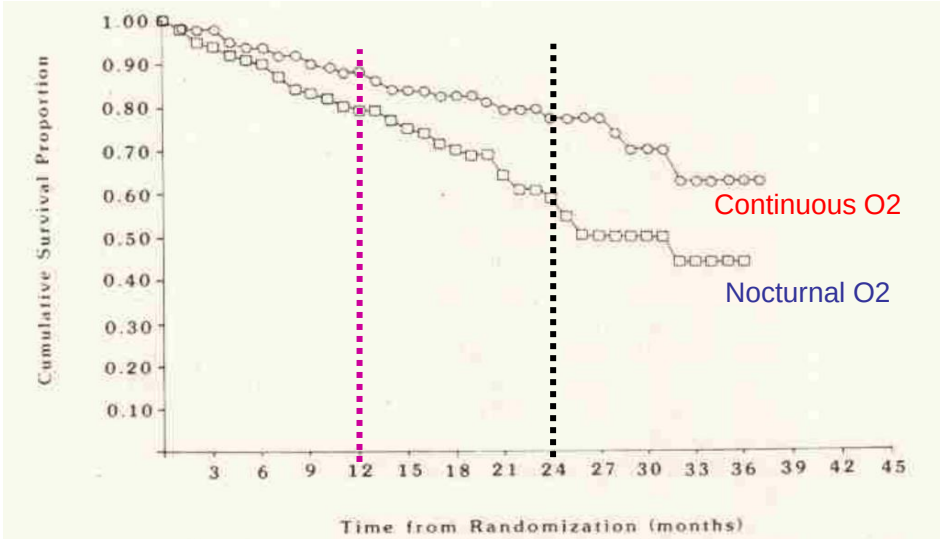

Figure 2. Overall mortality. Ordinate is fraction of patients surviving; abscissa is time from randomization or duration of treatment. Open circles represent continuous O_2 therapy group; squares represent nocturnal O_2 therapy group. Of the total group, 80 nocturnal O_2 and 87 continuous O_2 therapy patients were followed for 12 months, and 29 nocturnal O_2 and 37 continuous O_2 therapy patients were followed for 24 months.

Subjects with PCO2≥43mmHg

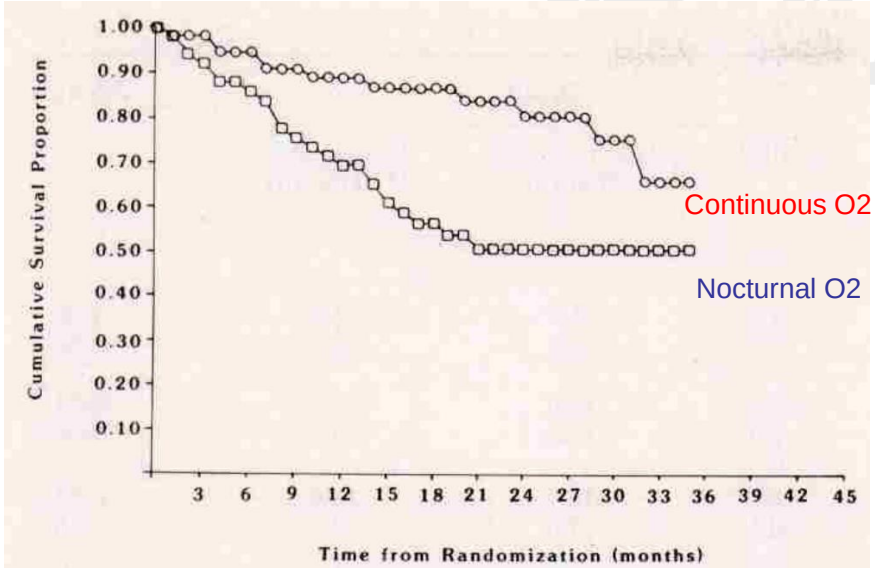

Figure 3. Survival of patients with arterial Pco_2 over 43 mm Hg. Ordinate is fraction of patients surviving; abscissa is time from randomization or duration of treatment. Open circles represent continuous O_2 therapy patients; squares represent nocturnal O_2 therapy patients. Of these patients, 35 nocturnal O_2 therapy patients and 50 continuous O_2 therapy patients were followed for 12 months, and 13 patients on nocturnal and 25 on continuous O_2 therapy were followed for 24 months.

	12-month mortality	24-month mortality
Nocturnal oxygen	20.6%	40.8%
Continuous oxygen	11.9%	22.4%

NOTT group, Ann Intern Med 1980;93:391-398

MRC trial

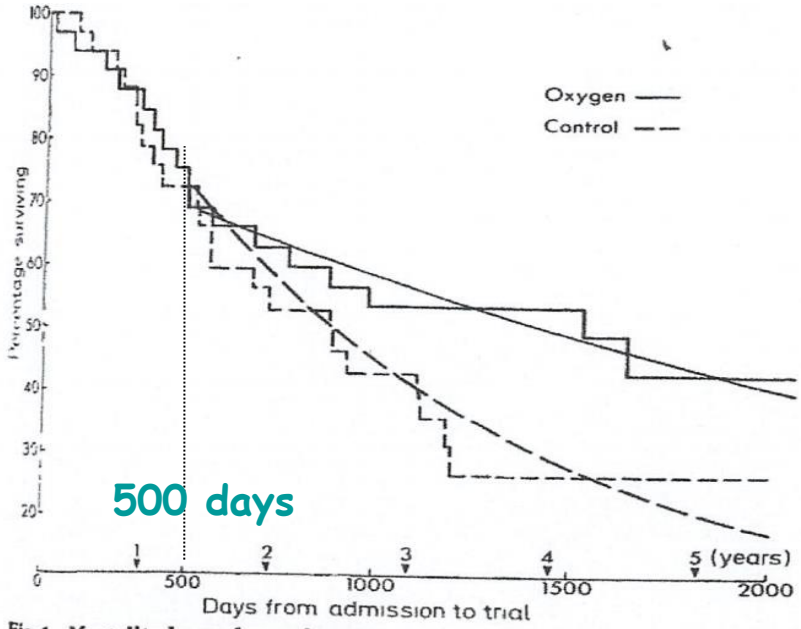

Fig. 1—Mortality in male patients.

Smooth curves indicate expected proportions surviving from 500 days, at constant risk of 11·9% per annum for those on oxygen, 29·4% per annum for the controls

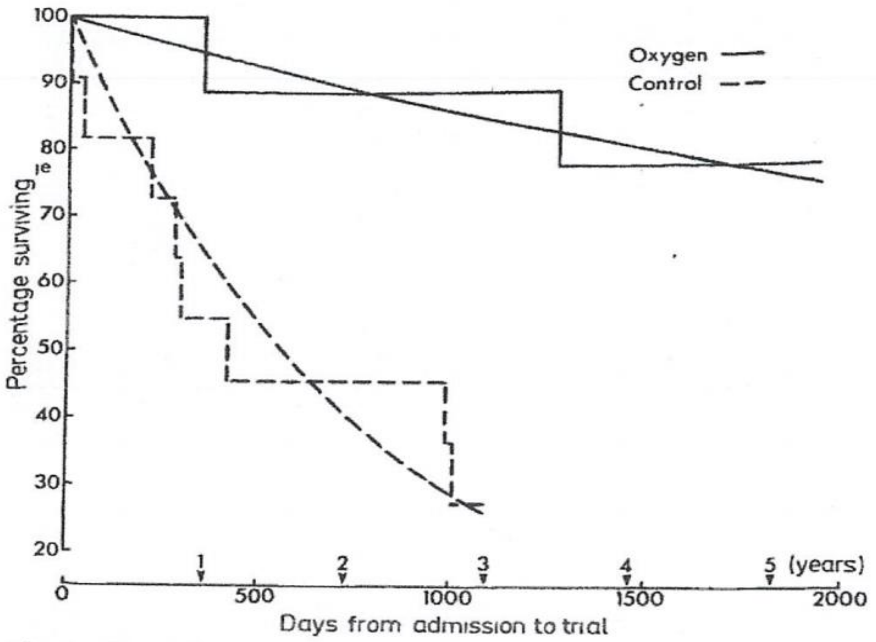

Fig. 2—Mortality in female patients.

Smooth curves indicate expected proportions surviving at constant risk of 5·7% per annum for those on oxygen, 36·5% per annum for the controls.

- Predicted 5-year survival rate in control group : 18%
- Annual risk of death for men: 12% in treatment group, 29% in control group
  - survival benefit of oxygen did not appear until after 500 days.

MRC working party, Lancet 1981;317:681-686

Effect of LTOT in moderate hypoxemic COPD patients

Outcome	Patient	Effect (95% CI)
Time to Death	Participants with moderate resting hypoxemia (either moderate resting hypoxemia only or moderate resting hypoxemia and desaturation during 6MWT)	Time to Death (LTOT vs No LTOT) HR: 0.94 (0.59 to 1.50)
St. George's Respiratory Questionnaire (SGRQ)	Participants with moderate resting hypoxemia only	SGRQ Total Score (LTOT vs No LTOT) 4 Months vs Baseline: MD -4.50 (-9.59 to 0.59) 12 Months vs Baseline :MD -2.90 (-8.58 to 2.78)
	Participants with moderate resting hypoxemia (either moderate resting hypoxemia only or moderate resting hypoxemia and desaturation during 6MWT)	SGRQ Total Score (LTOT vs No LTOT) 4 Months vs Baseline : MD -3.30 (-6.50 to -0.10)* 12 Months vs Baseline : MD -1.00 (-4.23 to 2.23)
Quality of Well-Being Scale (QWB)	Participants with moderate resting hypoxemia only	QWB Total Score (LTOT vs No LTOT) 4 Months vs Baseline : MD 0.04 (0.00 to 0.08) 12 Months vs Baseline : MD 0.00 (-0.06 to 0.06)
	Participants with moderate resting hypoxemia (either moderate resting hypoxemia only or moderate resting hypoxemia and desaturation during 6MWT)	QWB Total Score (LTOT vs No LTOT) 4 Months vs Baseline : MD -0.01 (-0.04 to 0.02) 12 Months vs Baseline : MD 0.01 (-0.03 to 0.05)

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AMERICAN THORACIC SOCIETY DOCUMENTS

Home Oxygen Therapy for Adults with Chronic Lung Disease

An Official American Thoracic Society Clinical Practice Guideline

Contents

Am J Respir Crit Care Med 2020;202:e121-e141

ATS guideline for COPD

Question	ATS Recommendation	Strength of Recommendation and Level of Evidence
COPD		
Question 1: Should long-term oxygen be prescribed for adults with COPD who have severe* chronic resting room air hypoxemia?	In adults with COPD who have severe chronic resting room air hypoxemia, we recommend prescribing LTOT for at least 15 h/d.	Strong recommendation, moderate-quality evidence
Question 2: Should long-term oxygen be prescribed for adults with COPD who have moderate† chronic resting room air hypoxemia?	In adults with COPD who have moderate chronic resting room air hypoxemia, we suggest not prescribing LTOT.	Conditional recommendation, low-quality evidence
Question 3: Should ambulatory oxygen be prescribed for adults with COPD who have severe exertional room air hypoxemia?	In adults with COPD who have severe exertional room air hypoxemia, we suggest prescribing ambulatory oxygen.	Conditional recommendation, moderate-quality evidence

Definition of abbreviations: ATS = American Thoracic Society; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; LTOT = long-term oxygen therapy.

*On the basis of two clinical trials (3, 4), severe hypoxemia is defined as meeting either of the following criteria: *1)* $Pa_{O_2} \leq 55$ mm Hg (7.3 kPa) or oxygen saturation as measured by pulse oximetry (Sp_{O_2}) ≤ 88% or *2)* Pa_{O_2} = 56–59 mm Hg (7.5–7.9 kPa) or Sp_{O_2} = 89% plus one of the following: edema, hematocrit ≥ 55%, or P pulmonale on an ECG.

†On the basis of a single clinical trial (5), moderate hypoxemia is defined as an Sp_{O_2} of 89–93%. The corresponding Pa_{O_2} was not reported in that study.

Am J Respir Crit Care Med 2020;202:e121-e141

ATS guideline for ILD

Question	ATS Recommendation	Strength of Recommendation and Level of Evidence
ILD		
Question 4: Should long-term oxygen be prescribed for adults with ILD who have severe chronic resting room air hypoxemia?	For adults with ILD who have severe chronic resting room air hypoxemia, we recommend prescribing LTOT for at least 15 h/d.	Strong recommendation, very-low-quality evidence
Question 5: Should ambulatory oxygen be prescribed for adults with ILD who have severe exertional room air hypoxemia?	For adults with ILD who have severe exertional room air hypoxemia, we suggest prescribing ambulatory oxygen.	Conditional recommendation, low-quality evidence

Definition of abbreviations: ATS = American Thoracic Society; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; LTOT = long-term oxygen therapy.

*On the basis of two clinical trials (3, 4), severe hypoxemia is defined as meeting either of the following criteria: *1*) $Pa_{O_2} \leq 55$ mm Hg (7.3 kPa) or oxygen saturation as measured by pulse oximetry (Sp_{O_2}) ≤ 88% or *2*) Pa_{O_2} = 56–59 mm Hg (7.5–7.9 kPa) or Sp_{O_2} = 89% plus one of the following: edema, hematocrit ≥ 55%, or P pulmonale on an ECG.

†On the basis of a single clinical trial (5), moderate hypoxemia is defined as an Sp_{O_2} of 89–93%. The corresponding Pa_{O_2} was not reported in that study.

Am J Respir Crit Care Med 2020;202:e121-e141

ATS guideline (3)

Question	ATS Recommendation	Strength of Recommendation and Level of Evidence
Liquid oxygen		
Question 6: Should portable liquid oxygen be provided for adults with chronic lung disease who are prescribed continuous oxygen flow rates of >3 L/min during exertion?	In patients with chronic lung disease who are mobile outside of the home and require continuous oxygen flow rates of >3 L/min during exertion, we suggest prescribing portable liquid oxygen.	Conditional recommendation, very-low-quality evidence
Education		
Education and safety for patients and caregivers	For all patients prescribed home oxygen therapy, we recommend that the patient and their caregivers receive instruction and training on the use and maintenance of all oxygen equipment and education on oxygen safety, including smoking cessation, fire prevention, and tripping hazards.	Best-practice statement

Definition of abbreviations: ATS = American Thoracic Society; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; LTOT = long-term oxygen therapy.

*On the basis of two clinical trials (3, 4), severe hypoxemia is defined as meeting either of the following criteria: *1*) $Pa_{O_2} \leq 55$ mm Hg (7.3 kPa) or oxygen saturation as measured by pulse oximetry (Sp_{O_2}) ≤ 88% or *2*) Pa_{O_2} = 56–59 mm Hg (7.5–7.9 kPa) or Sp_{O_2} = 89% plus one of the following: edema, hematocrit ≥ 55%, or P pulmonale on an ECG.

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Am J Respir Crit Care Med 202;202:e121-e141

산소치료 기기 대여료 지원 제도

산소치료(가정용·휴대용) 기기 대여료 지원제도 개요

지급대상

다음 각 호의 어느 하나에 해당하고, 공단에 환자등록을 신청한 사람

1. 중증의 만성심폐질환 등으로 산소치료가 필요하다고 인정되는 사람 중 90일 동안의 적절한 내과적 치료 후 별도로 시행한 동맥혈가스 검사 또는 산소포화도 검사 결과가 다음 각 목의 어느 하나에 해당하는 사람.
   다만, 90일 미만의 신생아 또는 장애정도가 심한 호흡기 장애인의 경우에는 내과적 치료없이 검사를 시행할 수 있다.

   가. 동맥혈가스 검사 결과가 다음의 어느 하나에 해당하는 경우
      1) 동맥혈 산소분압이 55mmHg 이하인 경우
      2) 동맥혈 산소포화도가 88% 이하인 경우
      3) 다음의 어느 하나에 해당하면서 적혈구 증가증(헤마토크릿이 55%를 넘는 경우를 말한다. 이하 같다)이 있거나, 울혈성 심부전을 시사하는 말초부종이 있거나, 폐동맥고혈압이 있는 경우
         가) 동맥혈 산소분압이 56~59mmHg인 경우
         나) 동맥혈 산소포화도가 89% 이상인 경우

   나. 산소포화도 검사 결과가 다음의 어느 하나에 해당하는 경우
      1) 산소포화도가 88% 이하인 경우
      2) 산소포화도가 89% 이상이면서 적혈구 증가증이 있거나, 울혈성 심부전을 시사하는 말초부종이 있거나, 폐동맥고혈압이 있는 경우

2. 2019.07.01.전 호흡기 1급 또는 2급 장애인이 확인되는 경우에는 제1호의 검사 없이 내과, 결핵과, 흉부외과 또는 소아청소년과 전문의가 산소치료가 필요하다고 판단한 사람

산소치료 기기 대여료 지원 제도 관련 상병

상병기호	상병명	상병기호	상병명
A150 ~ A169	호흡기결핵	I21 ~ I25	심근경색 관련 상병
B909	호흡기 및 상세불명 결핵의 후유증	I26 ~ I289	폐성심장병 및 폐순환의 질환
C32 ~ C349	기관지 및 폐의 악성 신생물	I500 ~ I509	울혈성 심부전 등
C73	갑상선의 악성 신생물	J43 ~ J47	폐기종 등
C780 ~ C783	폐의 이차성 악성 신생물	J60 ~ J65	진폐증 등
D021 ~ D022	기관의 제자리암종 등	J70	호흡기병태 및 폐장애 등
D1439	기관지 및 폐의 양성 신생물	J80 ~ J99	성인호흡곤란증후군 등
D382	흉막의 행동양식 불명 또는 미상의 신생물	P22 ~ P229	신생아의 호흡곤란
D384	흉선의 행동양식 불명 또는 미상의 신생물	P270 ~ P289	윌슨미키티증후군 등
R060 ~ R068	호흡곤란 등	Q20 ~ Q349	심방실 및 연결의 선천기형 등
하단 참고	폐렴 관련 상병		

※ A202, A403, A482, B012, B052, B206, B221, B250, B953, B960, B961, G001, G12, J12, J15, J16, J17, J18, J100, J101, J110, J120 ~ J129, J13, J14, J150 ~ 159, J160, J168, J170 ~ J178, J180, J181, J182, J188, J189, J200, J67, J69, J678, J679, J680, J690, J691, J698, J8410, J851, J852, M001, M0010 ~ M0019, O740, P23, P230 ~ P239

Exertional hypoxemia

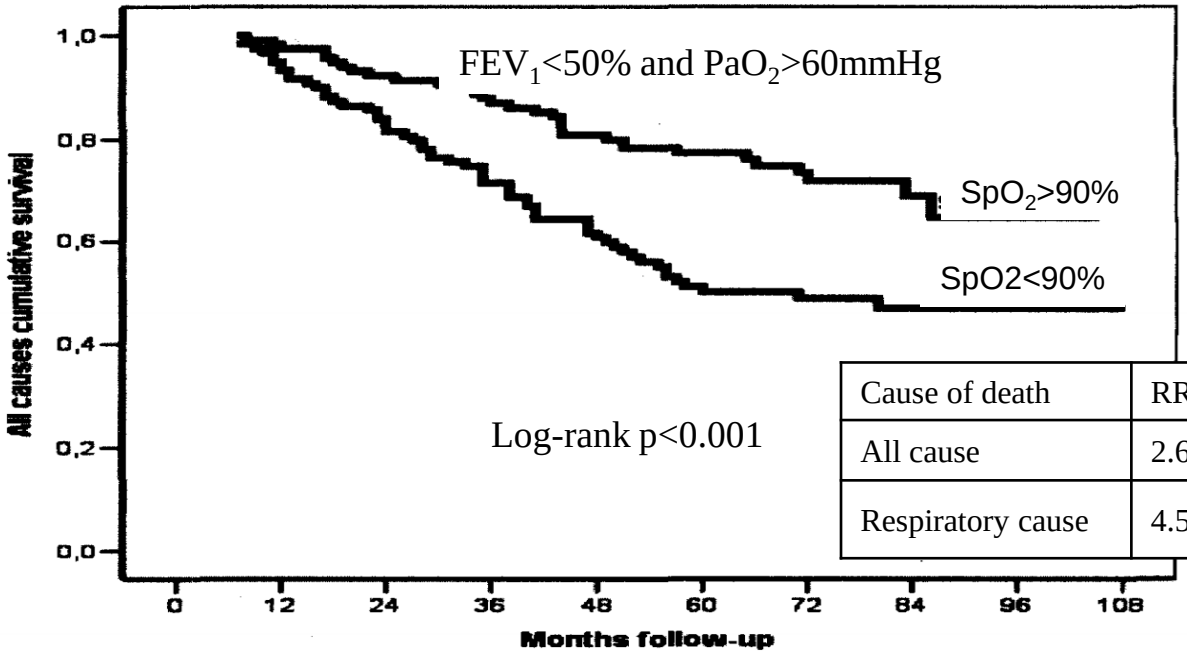
- Occurs in up to 40% of people with moderate to severe COPD who have normoxemia at rest

- Most frequently seen in those with
  - low lung function (FEV1<45%, DLCO<50%)
  - low resting saturation (<95%)
  - women

- Linked to
  - More rapid decline in lung function
  - Worse HRQL
  - Increased mortality
    - 2.63-fold higher mortality in those with isolated exertional hypoxemia on a 6MWT than in those without exertional hypoxemia (95% CI, 1.53-4.51)

Am J Respir Crit Care Med 2020;202:e121-e141

Oxygen desaturation during the 6MWT and all-cause mortality



Cause of death	RR ratio (95% CI)	p
All cause	2.625 (1.527-4.514)	<0.001
Respiratory cause	4.523 (2.23.5-9.152)	<0.001

Table 5—*Risk of Death From Any Cause and Respiratory Cause for Patients With FEV_1 < 50% of Predicted and Pao_2 ≥ 60 mm Hg According to Multivariate Logistic Binary Regression Modeling

Variables	All Causes			Respiratory Causes		
	RR Ratio	95% CI	p Value	RR Ratio	95% CI	p Value
6MWD 1 m less	1.006	1.003–1.009	< 0.001	1.007	1.002–1.011	0.002
Charlson score per unit increase	1.304	1.077–1.579	0.006	1.273	1.018–1.592	0.034
PaO_2 1 mm Hg less	1.052	1.012–1.092	0.010	1.073	1.021–1.126	0.005
FEV_1 % predicted 1% lower	1.045	1.006–1.086	0.022	1.063	1.014–1.115	0.011

*With constant using backward stepwise method and Wald criteria. Only factors that reached statistical significance at 0.05 level are shown.

CHEST 2008; 134:746-752

Ambulatory oxygen therapy (AOT)

- Oxygen delivered during exercise or activities of daily living when the individual is walking freely

- Purpose
  - To improve oxygen delivery during exertion
  - To reduce symptoms
  - To enhance physical capacity

- May be prescribed
  - for individuals using LTOT who require a portable oxygen supply when leaving the house
  - for those with isolated exertional hypoxemia

Am J Respir Crit Care Med 202;202:e121-e141

RCTs of AOT in patients with COPD qualifying for LTOT

Table 3. Randomized Trials of Ambulatory Oxygen Therapy in Patients with Chronic Obstructive Pulmonary Disease Qualifying for Long-Term Oxygen Therapy

Study	Population	Intervention/Comparator	Outcomes	Main Results
Vergeret *et al.* (60)	159 patients qualifying for LTOT	LTOT with stationary ($n = 75$) vs. LTOT + ambulatory oxygen therapy with cylinders ($n = 51$) vs. LTOT + ambulatory oxygen therapy with liquid oxygen ($n = 33$) (parallel study groups; 1 yr)	Primary: daily oxygen use, physical activity level	3-h difference in O_2 use with ambulatory oxygen therapy. No gain in physical activity with ambulatory oxygen therapy. No difference between cylinders and liquid oxygen.
Lacasse *et al.* (61)	24 patients qualifying for LTOT	LTOT with stationary equipment vs. LTOT with stationary equipment + ambulatory oxygen therapy vs. LTOT with stationary equipment + ambulatory compressed air (cross-over design, 3-mo treatment period)	Primary: disease-specific quality of life with the Chronic Respiratory Disease Questionnaire Secondary: 6-min-walk distance	No impact of ambulatory oxygen on quality of life or on 6-min-walk distance. No gain in daily exposure to oxygen.
Casaburi *et al.* (62)	22 patients qualifying for LTOT and using 10-kg E cylinders as ambulatory supply	LTOT with stationary equipment + 10-kg E cylinders ($n = 11$) vs. LTOT with stationary equipment + ambulatory oxygen therapy with 1.6-kg aluminum cylinders ($n = 11$) (parallel study groups; 6 mo)	Primary: daily oxygen use, physical activity level	No gain in oxygen use with ambulatory lightweight cylinders. No gain in activity levels with lightweight cylinders.

Definition of abbreviation: LTOT = long-term oxygen therapy.

Am J Respir Crit Care Med 2018;197:1254-1264

RCTs of AOT in patients with COPD not qualifying for LTOT

Study	Population	Intervention/Comparator	Outcomes	Main Results
Eaton *et al.* (64)	41 patients not qualifying for LTOT and with exercise-induced O_2 desaturation (Sp_{O_2}, ⩽88%)	Ambulatory oxygen therapy at 4 L/min with 2-kg cylinders vs. ambulatory compressed air with 2-kg cylinders (cross-over design, 6-wk treatment period)	Primary: disease-specific quality of life with Chronic Respiratory Disease Questionnaire	Statistically significant gain in quality of life with ambulatory oxygen
McDonald *et al.* (65)	26 patients not qualifying for LTOT	Ambulatory oxygen therapy with 5-kg cylinders at 4 L/min vs. ambulatory compressed air with 5-kg cylinders (cross-over design, 6-wk treatment period)	Primary: exercise capacity (6MWT, step test), quality of life with Chronic Respiratory Disease Questionnaire	No gain in step test or in quality of life with ambulatory oxygen therapy compared with compressed air. Statistically significant improvement in 6MWT (only on room air) of uncertain clinical significance (14 m).
Nonoyama *et al.* (66)	27 patients not qualifying for LTOT and with exercise-induced O_2 desaturation (Sp_{O_2}, ⩽88%)	Compressor + ambulatory oxygen therapy at 2 L/min with 2-kg cylinders vs. compressor + ambulatory placebo gas mixture (FI_{O_2}, 21%) with 2-kg cylinders (*n*-of-1 trials, 2-wk treatment period)	Primary: disease-specific quality of life with Chronic Respiratory Disease Questionnaire and SGRQ Secondary: 5-min-walk distance	No gain in quality of life with ambulatory oxygen therapy compared with compressed air. Statistically significant improvement in 5MWT of uncertain clinical significance (15 steps over 5 min).
Moore *et al.* (67)	143 patients not qualifying for LTOT and with severe exertional dyspnea	Ambulatory oxygen therapy at 6 L/min with 4.2-kg cylinders ($n = 68$) vs. ambulatory compressed air with 4.2-kg cylinders ($n = 75$) (parallel study groups, 12-wk treatment period)	Primary: dyspnea domain of the Chronic Respiratory Disease Questionnaire Secondary: health-related quality of life, 6MWT, TDI score, physical activity	No gain in dyspnea domain of Chronic Respiratory Disease Questionnaire with ambulatory oxygen therapy compared with compressed air. No gain in quality of life, dyspnea, 6MWT, or physical activity with ambulatory oxygen therapy compared with compressed air.

for any activity during which they would normally experience dyspnoea

home using exertional cylinder air or oxygen

use the gas provided for at least 1 hour per day during activities that made them short of breath.

to use cylinders inside and outside the home during exertional activities that induced breathlessness

Am J Respir Crit Care Med 2018;197:1254-1264

Ambulatory O2 for COPD patients with isolated exertional desaturation

Definition of exertional hypoxemia : an SpO2≤88%

Outcome		N	Effect, O2 vs. cylinder air (95% CI)
CRQ	fatigue score	132	SMD 0.84 (-0.15 to 2.21)
	emotion score	132	SMD 1.32 (-1.10 to 3.74)
	majesty score	132	SMD 0.58 (-1.02 to 2.17)
	Dyspnea-Related Quality of Life Score	132	SMD 0.42 (0.04 to 0.79)
SGRQ	Total score	27	MD -0.32 (-1.71 to1.06)
SF-36	role physical score	41	MD 16.8 (6.02to 27.58)
	general health score	41	MD 6.1 (0.42 to 11.78)
	social functioning score	41	MD: 10.5 (0.31 to 20.69)
	role emotional score	41	MD: 18.3 (3.21 to 33.39)
	physical functioning score	41	MD: 1.6 (-5.26 to 8.46)
	bodily pain score	41	MD: 5.3 (-4.50 to 15.10)
	vitality score	41	MD: 2.9 (-2.98 to 8.78)
	mental health score	41	MD: 4.0 (-1.29 to 9.29)

Am J Respir Crit Care Med 202;202:e121-e141, online supplement

Ambulatory O2 for COPD patients with isolated exertional desaturation

Outcome		N	Effect (95% CI)
5-Minute Walk Test	Number of steps walked	27	O2 vs. CA, MD: 14.90 (0.85 to 28.94)*
	Endurance time, mins	27	O2 vs. CA, MD: 2.40 (0.58 to 4.22)*
6-Minute Walk Test	Distance walked, m	84	O2 vs. CA, MD: 28.99 (16.06 to 41.92)*
Maximal Exercise	Work, watts,	17	O2 vs. RA, MD: 7.6 (-6.8 to 22.0)
Exercise Tolerance	Time to Exercise Tolerance, minutes	15	O2 vs. RA, MD: MD: 5.8 (2.23 to 9.37)*
Symptom-Limited Low-Level Incremental Exercise	Work, watt	14	O2 vs. RA, MD: 17.9 (8.10 to 27.70)*
Dyspnea	Borg Dyspnea Score	99	O2 vs. control, MD: -1.11 (-1.69 to -0.59)*

- No studies reported the long-term effects of ambulatory oxygen on exercise capacity beyond acute laboratory or field tests, and no studies reported effects on physical activity in daily life.
- MCID for Borg dyspnea Score : 0.9 unit

Am J Respir Crit Care Med 202;202:e121-e141, online supplement

Ambulatory O2 for COPD patients with resting hypoxemia and severe exertional desaturation

Outcome		N	Effect (95% CI)
6-Minute Walk Test	Distance walked, m	13	O2 vs. CA, MD: 25.00 (-44.34, 94.34)
Incremental Shuttle Walk Test (ISWT)	Distance walked, m	22	O2 vs. RA, MD: 27.3 (14.7 to 39.8)*
	Endurance time, s	22	O2 vs. RA, MD: -23.6 (-70.7 to 23.5)
Maximum Distance Walked	m	21	O2 vs. CA, MD: 88.0 (-23.14 to 199.14)
Symptom-Limited Peak Exercise	minutes	11	O2 vs. RA, MD: 4.70 (3.76 to 5.64)*
Dyspnea	Borg Dyspnea Score	46	O2 vs. control, MD: MD: -0.59 (-0.99 to -0.18)*

- None included results for HRQL.
- No studies examined safety in patients with COPD using only ambulatory portable oxygen systems.

- MCID for Borg dyspnea Score : 0.9 unit

Am J Respir Crit Care Med 202;202:e121-e141, online supplement

Indication of AOT for COPD patients

- AOT should only be offered to patients already on LTOT if they are[29]
  - Mobile outdoors (so they can achieve the required duration of daily usage), or
  - Too symptomatic to leave home without AOT.
- Two of 3 of the following criteria should be met to prescribe AOT (expert consensus, no solid evidence):[29]
  - SpO2 can be kept constantly >90% during exercise with oxygen
  - Improvement of 6MWT by ≥10%
  - Improvement of dyspnea (≥1 point improvement on the Borg scale)
- Regarding patients with COPD with exercise-induced desaturation who do not have the classic criteria at rest:
  - They probably do not benefit from AOT regarding mortality, exercise capacity or dyspnea during exercise[18,90,91]
  - Because AOT transiently improves their exercise capacity,[92] they should get AOT as part of a rehabilitation program.[23,29,30]

Clin Chest Med 2020;41: 529-545

Ambulatory O2 for ILD patients with isolated exertional desaturation

Definition of exertional hypoxemia : an SpO2≤88%

Outcome		N	Effect, O2 vs. cylinder air (95% CI)
King's Brief Interstitial Lung Disease (K-BILD) Score	Total Score	76	MD: 3.7 (1.8 to 5.6)*
	Breathlessness/Activities Score	76	MD: 8.6 (4.7 to 12.5)*
	Chest Symptoms	76	MD: 7.6 (1.9 to 13.2)*
	Psychological Symptoms	76	MD: 2.4 (–0.6 to 5.5)
SGRQ	Total score	76	MD: -3.6 (-6.7 to -0.6)*
Dyspnea	Borg Dyspnea Score	136	O2 vs. control, MD: -0.72 (-1.70 to 0.27)
	UCSD SOB Q	76	MD: -8.0 (-12.4 to -3.6)*

- MCID for UCSD SOB Questionnaire : 5 units
- MCID for K-BILD score : 5 units

Am J Respir Crit Care Med 202;202:e121-e141, online supplement

Ambulatory O2 for ILD patients with isolated exertional desaturation

Outcome	N	Effect, 95% CI
6-Minute Walk Test Distance (m)	136	O2 vs. control, MD: 18.57 (11.16 to 25.59)*.
6-Minute Walk Test Endurance Time (S)	72	O2 vs. RA, MD: 118.70 (24.71 to 212.69) *
Maximum Work Rate (watts)	13	O2 vs. RA, MD: 10.34 (-3.59 to 24.25)
Exercise Duration (s)	13	O2 vs. RA, MD: 57.67 (0.22 to 115.12)*
Endurance Shuttle Walk Test Distance (ESWT, m)	6	O2 vs. RA, MD: 265.00 (-297.88 to 827.88)
Composite Index (Borg Fatigue Score)	136	O2 vs. control, MD: -0.37 (-0.54 to -0.19)*

- No studies reported the effects of ambulatory oxygen on fatigue, exercise capacity in the long term, physical activity in daily life, or mortality.
- MCID for Borg Fatigue Score : 1 unit

Am J Respir Crit Care Med 202;202:e121-e141, online supplement

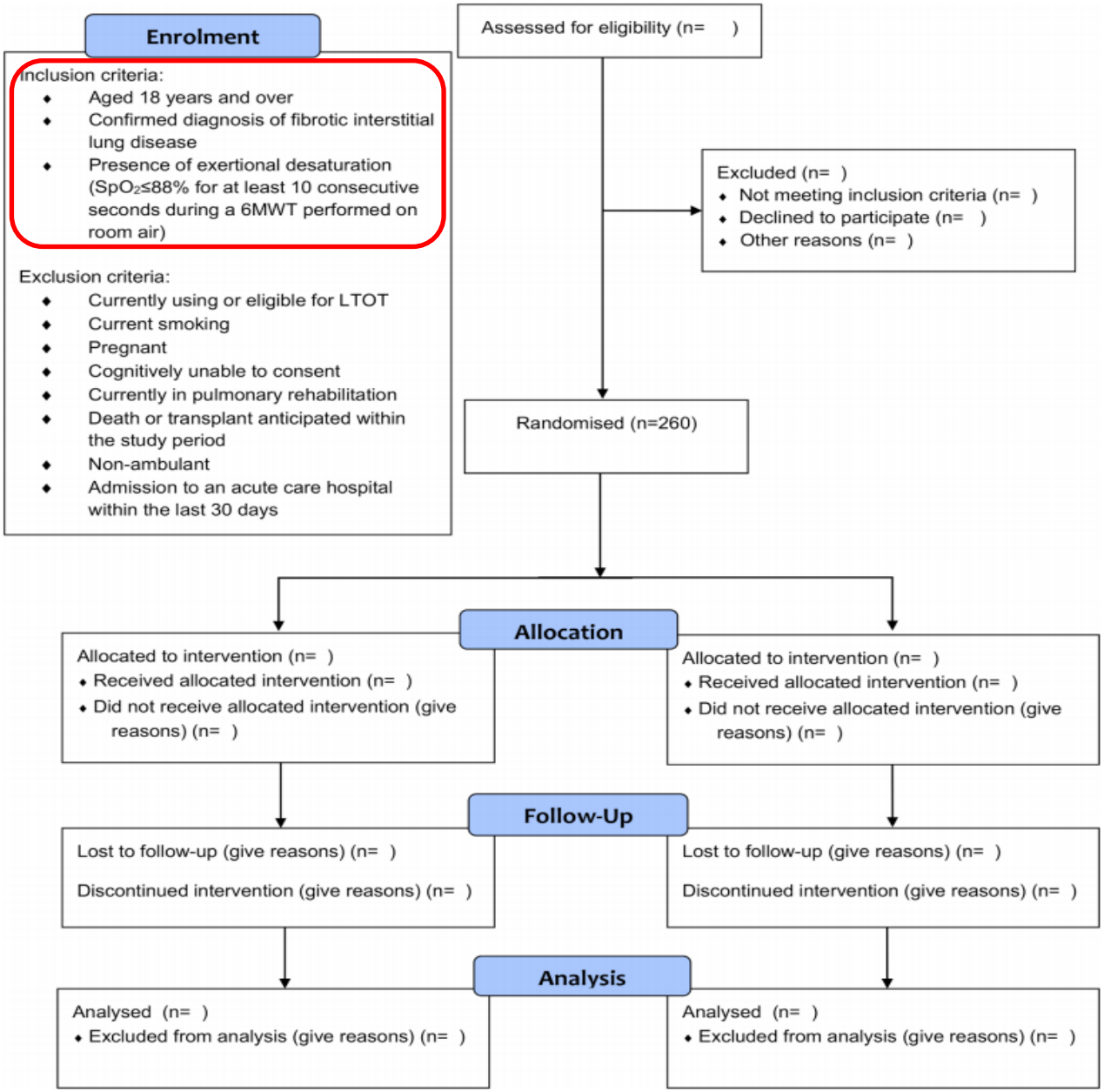
Open access Protocol

BMJ Open

Ambulatory oxygen for treatment of exertional hypoxaemia in pulmonary fibrosis (PFOX trial): a randomised controlled trial

Anne E Holland ,[1,2,3,4] Tamera Corte,[4,5,6] Daniel C Chambers,[4,7,8] Andrew J Palmer,[4,9,10] Magnus Per Ekström,[11] Ian Glaspole,[2,4,12] Nicole S L Goh,[3,13,14] Graham Hepworth,[15] Yet H Khor,[3,12,13,14] Mariana Hoffman,[2] Ross Vlahos,[16] Magnus Sköld,[17,18] Leona Dowman,[2,3,14,19] Lauren K Troy,[5,6] Jyotika D Prasad,[12,20] James Walsh,[21] Christine F McDonald[3,13,14]

BMJ Open 2020;10:e040798.



The primary outcome :

- change in physical activity, measured by the number of steps per day

All participants will be encouraged to use the POC at all times when they are moving about, including walking at home or in the community, during exercise or during other activities.

The POC should not be used when sitting still or sleeping.

BMJ Open 2020;10:e040798.

Ambulatory oxygen therapy

Source	Recommendations
ATS (2020)	• In adults with **COPD who have severe exertional room air hypoxemia**, we suggest prescribing ambulatory oxygen. (Conditional recommendation, moderate-quality evidence) • For adults with **ILD who have severe exertional room air hypoxemia**, we suggest prescribing ambulatory oxygen.(Conditional recommendation, low-quality evidence)
BTS (2015)	• AOT should not be routinely offered to patients who are not eligible for LTOT. (Grade B) • AOT should not be routinely offered to patients already on LTOT. (Grade D) • AOT assessment should only be offered to patients already on LTOT if they are mobile outdoors. (Grade A) • AOT should be offered to patients for use during exercise in a pulmonary rehabilitation programme or during an exercise programme following a formal assessment demonstrating improvement in exercise endurance. (Grade B)
TSANZ (2016)	• Patients on LTOT who are active outside the home and wish to maximize their duration of oxygen therapy. (GRADE recommendation: strong; evidence: very low). • Patients do not have resting hypoxaemia severe enough to warrant LTOT but are breathless and desaturate on exertion (GRADE recommendation: weak; evidence: very low).
German (2008)	• AOT should be prescribed to LTOT patients with classic indication parameters and who are mobile outdoors. • Recommends AOT for patients who do not meet the classic indication criteria if PaO2 is ≤ 60mmHg at rest and drops by more than 5mmHg to less than 55mmHg during ergometric assessment, or if AOT substantially improves exercise performance.

Statements about oxygen therapy in various Korean guidelines

진료지침	내용
COPD (2018)	• 안정상태에서 중증 저산소혈증을 동반한 만성호흡부전 환자에게 장기간 산소투여(하루 15시간 이상)는 생존율 향상 을 보였다184. 장기산소요법은 다음과 같은 환자에게 적용한다. (1) 고탄산혈증 여부와 관계없이 동맥혈산소분압(PaO2)이 최소 55 mmHg 이하이거나 산소포화도(SaO2)가 88% 이하; 혹은 (2) 동맥혈산소분압이 55 mmHg와 60 mmHg 사이거나 산소포화도가 89%이면서 폐고혈압, 울혈성심부전을 암시하는 말초부종, 혹은 적혈구증가증(적혈구용적률 > 55%)이 보이는 경우
폐고혈압 (2020)	• 산소 투여가 폐혈관저항을 감소시키는 것은 확인되었지만, 장기적인 산소투여 요법이 폐동맥고혈압 환자에서 유익하다는 것을 보여 주는 무작위 연구 결과는 없다. • 현재의 대다수 진료지침은 만성폐쇄폐질환 환자의 연구 결과에 기초해 동맥혈 산소 분압이 일관되게 < 60 mmHg (8 kPa), 또는 동맥혈 산소포화도가 91% 이하인 경우, 동맥혈 산소 분압을 60 mmHg 이상으로 유지하 기 위해 산소를 투여하는 것을 권장한다. • 운동 시 증상 개선과 산소 포화도 감소를 교정하기 위해 휴대용 산소를 고려할 수 있다.
Asthma (2020)	• 언급 없음
ILD (2018)	• 언급 없음

Add-on interventions during pulmonary rehabilitation

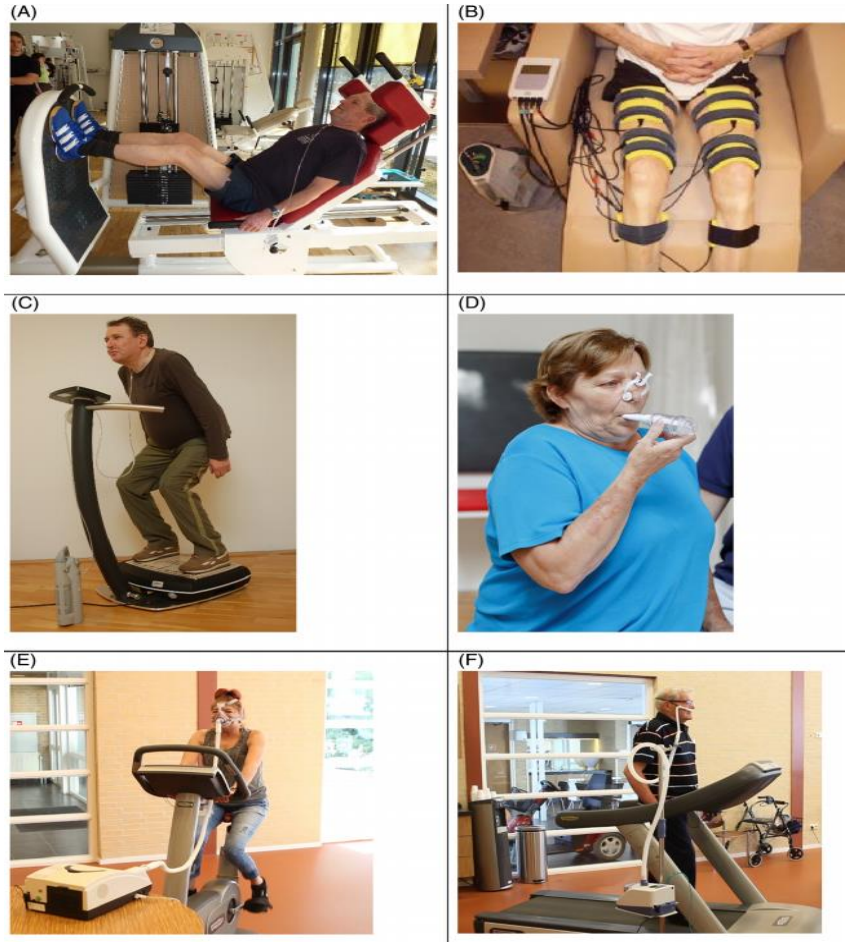


Figure 1 Tools for individualizing exercise programmes: (A) resistance training, (B) neuromuscular electrical stimulation, (C) whole-body vibration training, (D) inspiratory muscle training, (E) non-invasive ventilation and (F) nasal high-flow oxygen supplementation.

Figure 1.
A patient during the training session (with permission).

Respirology 2019 24: 899-908

Phys Ther. 2020;100:1249–1259

RCTs For O2 Therapy For Pulmonary Rehabilitation and Exercise Training in COPD Patients

Study population	Comparison (n recruited/ Completed the study)	Resting FEV_1 (L and/or % predicted)	Resting PaO_2 (mmHg)	Resting SaO_2	Training type	Training duration	Impact on outcomes
Rooyackers[66] 1997 Patients with SaO_2 <90% at the peak incremental cycle exercise	Oxygen 4 L/min (12/12)	0.9 L (29%)	77	NA	In-patient pulmonary rehabilitation program (general exercise training included dynamic and isometric strength training and specific training of daily life activities like breathing retraining, physical therapy)	80 minutes 5x/week 10 weeks	Primary outcome: Although supplemental oxygen had acute beneficial effects on exercise performance, oxygen-supplemented exercise training did not add to the effects of training while breathing room air. Secondary outcomes: Pulmonary rehabilitation improved exercise performance and quality of life (assessed with CRQ) in both groups.
	Room air (12/12)	1.2 L (38%)	79	NA			
Fichter[67] 1999 Patients with stable disease	Oxygen 35% (5/5)	43.2%	74	NA	Cycle ergometer training at a constant workload of 80% of their highest achieved work-rate	45 minutes 5x/week 4 weeks	Primary outcome: Change in maximally achieved power in the incremental exercise test after training was 15.9% in the supplemental oxygen group and 36.3% in room air group
	Room air (5/5)						
Garrod[68] 2000 Patients with limited exercise tolerance due to dyspnea and having a fall in arterial saturation of at least 4% from baseline to 90% or below upon exercise testing	Oxygen 4 L/min (13/11)	0.77 L (28.5%)	64	92%	Upper and lower limb training	60 minutes 3x/week 6 weeks	Primary outcome: There was no l benefit of oxygen on exercise tolerance or health status (no change in SWT, CRQ, HAD or London Chest Activity of Daily Living scales) Secondary outcome: The supplemental oxygen group had a greater reduction in dyspnea upon exertion, as measured with the Borg scale compared with the air group
	Compressed air (12/11)	0.84 L (35.0%)	64	93%			
Wadell[69] 2001 Patients with PaO_2 >60 mmHg at rest and hypoxemia during exercise (SaO_2 ≤92% in the 6MWD)	Oxygen 5 L/min (11/10)	39.3%	71	95%	Interval walking on a treadmill (intensity set according to Borg ratings)	30 minutes 3x/week 8 weeks	Primary outcome: Supplemental oxygen did not improve the training effect compared with training with air Secondary outcomes: Training significantly improved distance in 6MWT in both groups. Oxygen group showed no decrease in Borg ratings for dyspnea, higher increase in lactate during exercise after training and increase in time for SaO2<90% during the test
	Compressed air (11/10)	51.6%	70	95%			
Emtner[70] 2003 Patients who do not experience appreciable desaturation during exercise (SpO_2 ≥88% during a constant work rate test)	Oxygen 3 L/min (15/14)	1.0 L (35%)	72	94%	High-intensity endurance training with a cycle ergometer	45 minutes 3x/week 7 weeks	Primary outcome: Supplemental oxygen group achieved higher training intensity and endurance capacity and the breathing pattern improved significantly Secondary outcome: Quality of life (assessed with CRQ) increased significantly in both groups
	Compressed air (15/15)	1.0 L (38%)	74	93%			

COPD 2017; 14:351-366

RCTs For O2 Therapy For Pulmonary Rehabilitation and Exercise Training in COPD Patients

	Study population	Comparison (n recruited/ Completed the study)	Resting FEV_1 (L and/or % predicted)	Resting PaO_2 (mmHg)	Resting SaO_2	Training type	Training duration	Impact on outcomes
Scorsone[71] *2010*	Patients with FEV_1 <60% predicted	Oxygen 40% (10/10)	47%	74	NA	Leg-cycle training at 80% of the initial peak work rate for at least 20 minutes	40 minutes 3x/week 8 weeks	Primary outcome: Supplemental oxygen and heliox did not provide an advantage for improving exercise tolerance and symptoms over air
		Humidified air (10/10)	50%	76	NA			Secondary outcomes: Physical training resulted in a significant improvement in peak oxygen consumption, power output and exercise endurance time in all groups
		Heliox $_{60-40}$ (10/10)	49%	77	NA			
Dyer[72] *2012*	Patients desaturated by >4% and to <90% upon exertion, and walked 10% or more further with ambulatory oxygen on ESWT	Oxygen 2-6 L/min to keep SpO_2 >90% (28/24)	0.96 L (39%)	NA	94%	Strengthening and endurance exercise tailored to suit individual needs with aerobic exercise (walking) set at 85% the estimated peak oxygen uptake together with an education program	2x/week 6-7 weeks	Primary outcome: Supplemental oxygen significantly improved the endurance walking distance during pulmonary rehabilitation program
		Room air (27/23)	1.12 L (44%)	NA	94%	Home exercise program: Participants randomized to the oxygen group were asked to use oxygen at their prescribed flow rate at home during all activities that induced dyspnea		Secondary outcome: There was no statistically significant change in quality of life (assessed with CRQ, HAD scale, SIFT questionnaire)
Ringbaek[73] *2013*	Patients desaturated by >4% and <90% during ESWT	Oxygen 2 L/min (22/12)	32.8 %	NA	94%	Supervised walking and cycling and unsupervised home training (patients were instructed to continue the unsupervised training at home at least 30 min every day during the whole study period)	1st phase: 30 minutes 2x/week for 7 weeks; 2nd phase: 30 minutes 1x/week for 12 weeks; 3rd phase: Only unsupervised home training at least 30 minutes for 12 weeks	Primary outcome: Supplemental oxygen improved oxygen saturation during ESWT but there was no difference between the groups at 33-weeks of evaluation with regard to the change in ESWT
		Control (23/17)	10.9%	NA	94%	Participants randomized to the oxygen group were asked to use oxygen during supervised and unsupervised training		Secondary outcomes: Oxygen therapy did not provide an additional benefit in terms of quality of life (assessed with SGRQ), risk of acute exacerbations and hospitalizations
Spielmanns[74] *2014*	Patients who were normoxemic (SaO_2 >90%) at rest and during exercise without an oxygen supply	Oxygen 4 L/min (42/19)	1.2 L (44%)	NA	> 90%	Endurance training program with progressively increasing loads involving large muscle groups	30 min 3x/week 24 weeks	Primary outcome: Supplemental oxygen during the training program did not result additional change in 6MWT distance
		Compressed air (43/17)	1.5 L (43%)					Secondary outcomes: Endurance training resulted in significant improvements in quality of life (assessed with SF-36) and exercise capacity in subjects with moderate-to-severe COPD

COPD 2017; 14:351-366

STUDY PROTOCOL Open Access

A randomised controlled trial of supplemental oxygen versus medical air during exercise training in people with chronic obstructive pulmonary disease: supplemental oxygen in pulmonary rehabilitation trial (SuppORT) (Protocol)

Jennifer A Alison[1,2*], Zoe J McKeough[1], Sue C Jenkins[3,4,5], Anne E Holland[6,7,8], Kylie Hill[3,5], Norman R Morris[9,10], Regina WM Leung[1,11], Kathleen A Williamson[1], Lissa M Spencer[2], Catherine J Hill[8,12], Annemarie L Lee[7,8], Helen Seale[10], Nola Cecins[4] and Christine F McDonald[8,13,14]

ORIGINAL ARTICLE
COPD

Oxygen compared to air during exercise training in COPD with exercise-induced desaturation

Jennifer A. Alison[1,2], Zoe J. McKeough[1], Regina W.M. Leung[3], Anne E. Holland[4,5,6], Kylie Hill[7,8], Norman R. Morris[9,10], Sue Jenkins[7,8,11], Lissa M. Spencer[12], Catherine J. Hill[6,13], Annemarie L. Lee[14], Helen Seale[15], Nola Cecins[11] and Christine F. McDonald[6,16]

BMC Pulm Med_2016;16:25

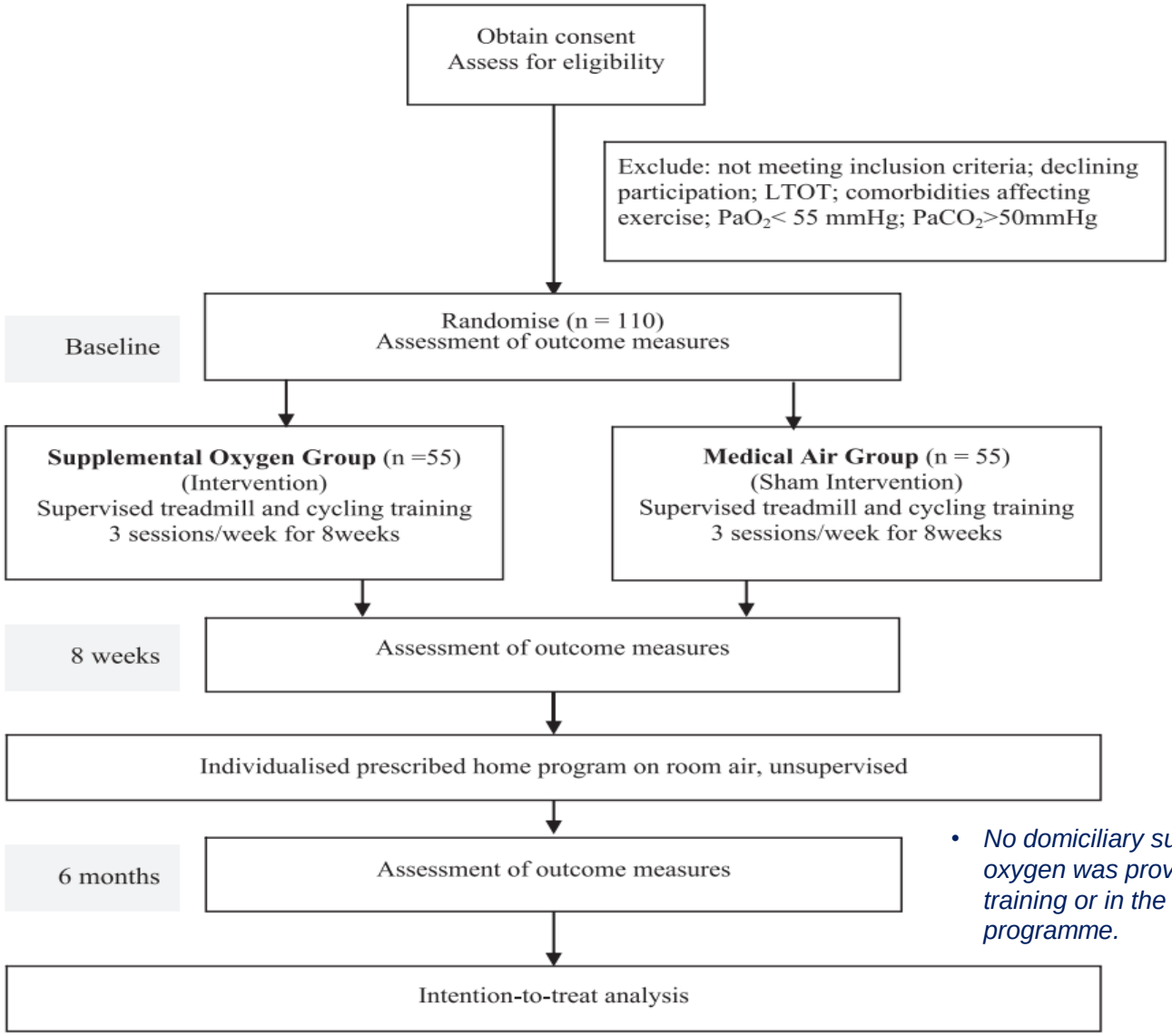
Eur Respir J 2019; 53: 1802429

Study design

- A prospective, multi-centre, randomized controlled trial with concealed allocation, blinding of participants, therapists and assessors and with intention-to treat analysis
- Eligible Participants
  - COPD patients with >10 PY smoking Hx
  - Medically stable - at least 4weeks post an exacerbation
  - Evidence of oxygen desaturation to less than 90 % during the 6MWT performed on room air
- Primary Outcome measures
  - Endurance exercise capacity : endurance shuttle walk test (ESWT)
  - HRQoL : Chronic Respiratory Disease Questionnaire (CRQ)-Total score

at baseline, the completion of exercise training and 6 months following completion of the exercise training program

BMC pulm Med 2016; 16:25



- *No domiciliary supplemental oxygen was provided during the training or in the 6-month home programme.*

Fig. 1 Flow of participants through the trial. LTOT = long term oxygen therapy

Summary of primary outcomes

	at end-training		At 6-month follow-up	
	Between group comparison (Oxygen vs. Air)	Within group	Between group comparison (Oxygen vs. Air)	Within group
change in ESWT time	No difference observed	Showed significant improvements in both groups	No difference observed	Showed nonsignificant improvements in both groups
change in CRQ-Total score	No difference observed	Showed significant improvements in both groups	No difference observed	Showed significant improvements in both groups

Eur Respir J 2019; 53: 1802429

Primary outcomes

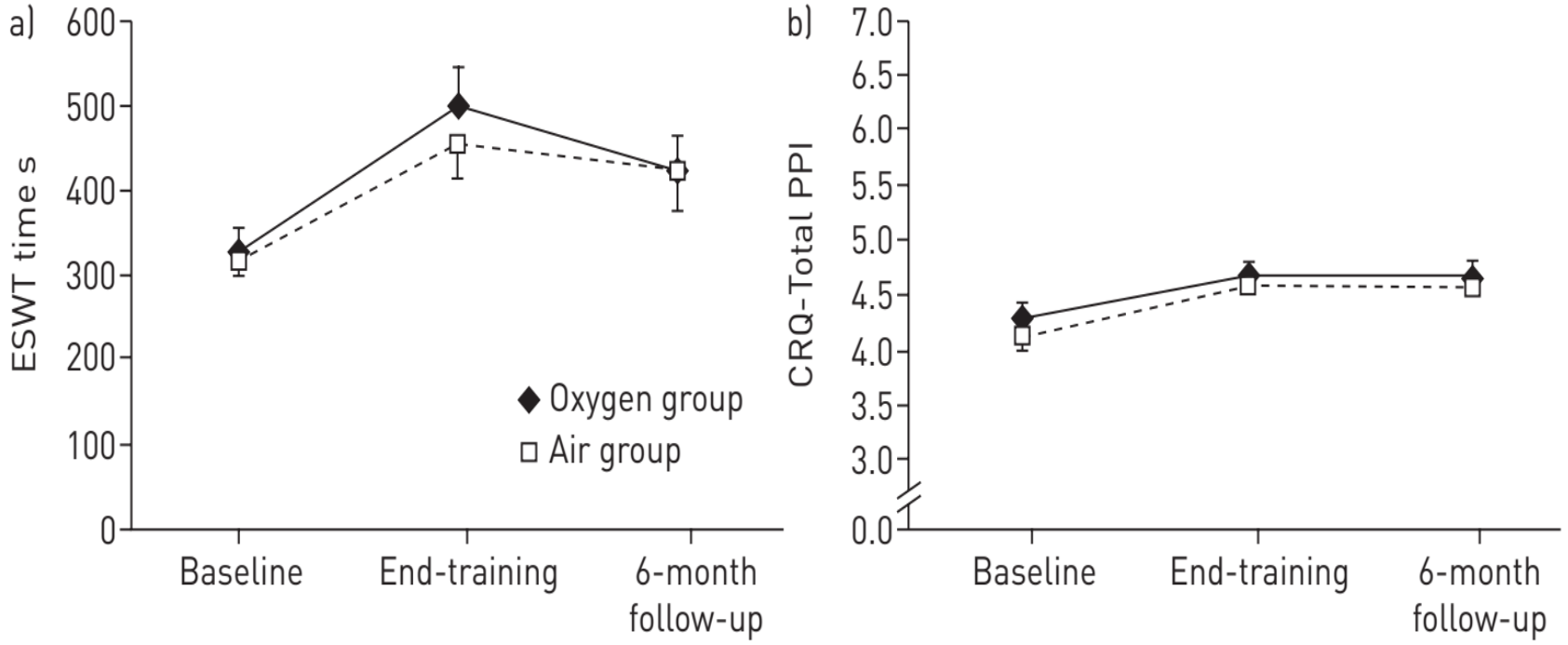


FIGURE 2 Change in a) endurance shuttle walk test (ESWT) time and b) Chronic Respiratory Disease Questionnaire (CRQ)-Total in the Oxygen and Air groups. PPI: points per item. Data are presented as mean±SE.

Eur Respir J 2019; 53: 1802429

Within-group and between group analyses

TABLE 3 Within-group and between-group statistical analyses

	Within-group difference from baseline				Between-group difference (Oxygen group–Air group)	
	Oxygen group		Air group			
	End-training	6-month follow-up	End-training	6-month follow-up	End-training	6-month follow-up
ESWT						
Time s	162 (80–244)*	76 (−16–169)	147 (59–235)*	91 (−4–187)	15 (−106–136)	−15 (−148–118)
Dyspnoea isotime score#	−1.2 (−1.6–−0.8)*		−0.9 (−1.4–−0.4)*		−0.3 (−0.3–0.9)	
RPE isotime score	−1.2 (−1.7–−0.7)*		−1.1 (−1.6–−0.5)*		−0.2 (−0.6–0.9)	
ISWT						
Distance m	33 (20–47)*	24 (9–39)*	28 (13–42)*	15 (−1–30)	5 (−14–25)	9 (−12–31)
Dyspnoea isotime score¶	−0.9 (−1.2–−0.5)*		−0.3 (−0.7–0.1)		−0.6 (−1.2–−0.1)**	
CRQ						
Total PPI	0.4 (0.2–0.7)*	0.3 (0.1–0.5)*	0.4 (0.2–0.7)*	0.4 (0.1–0.6)*	0.0 (−0.3–0.3)	−0.0 (−0.4–0.3)
Dyspnoea PPI	0.7 (0.4–1.0)*	0.6 (0.3–0.9)*	0.6 (0.3–0.9)*	0.6 (0.3–0.9)*	0.1 (−0.3–0.5)	0.004 (−0.5–0.5)
Fatigue PPI	0.6 (0.3–0.9)*	0.3 (0.01–0.7)*	0.5 (0.2–0.9)*	0.3 (−0.01–0.7)	0.03 (−0.4–0.5)	−0.01 (−0.5–0.5)
Emotional Function PPI	0.4 (0.1–0.6)*	0.2 (−0.0–0.5)	0.2 (−0.0–0.5)	0.3 (0.01–0.6)*	0.2 (−0.2–0.5)	−0.1 (−0.4–0.3)
Mastery PPI	0.3 (0.0–0.5)*	0.3 (0.0–0.6)*	0.3 (0.1–0.6)*	0.1 (−0.2–0.4)	−0.1 (−0.5–0.3)	0.2 (−0.2–0.6)
Dyspnoea-12						
Total score	−2.3 (−4.0–−0.5)*	−0.7 (−2.6–1.2)	−0.3 (−2.2–1.6)	0.2 (−1.8–2.3)	−1.9 (−4.5–0.7)	−0.9 (−3.7–1.9)
Physical score	−1.5 (−2.7–−0.4)*	−0.5 (−1.8–0.7)	−0.3 (−1.6–0.9)	0.7 (−0.7–2.0)	−1.2 (−2.9–0.5)	−1.2 (−3.1–0.6)
Affective score	−0.8 (−1.6–0.1)	−0.2 (−1.2–0.7)	0.1 (−0.8–1.0)	−0.4 (−1.4–0.6)	−0.9 (−2.2–0.4)	0.2 (−1.2–1.6)
Physical activity						
Steps·day^{-1}	57 (−277–391)	146 (−233–524)	−283 (−654–87)	462 (34–889)*	340 (−157–839)	−316 (−887–255)
Total EE·day^{-1} kcal	−35 (−109–40)	−55 (−139–29)	24 (−58–107)	−51 (−147–45)	−59 (−171–53)	−4 (−132–125)
Sedentary+ min·day^{-1}	7 (−24–38)	12 (−23–46)	−10 (−44–25)	−13 (−52–26)	16 (−30–63)	25 (−27–77)
Light activity§ min·day^{-1}	−27 (−47–−8)	−1 (−23–22)	−21 (−43–1)	8 (−17–34)	−6 (−36–24)	−9 (−43–25)
Moderate activityf min·day^{-1}	3 (−3–8)	−3 (−9–3)	−0 (−6–6)	−1 (−8–6)	3 (−6–11)	−2 (−11–8)
Vigorous activity## min·day^{-1}	−1 (−2–1)	−1 (−3–−0)	0 (−1–1)	−1 (−2–1)	−1 (−2–1)	−1 (−3–1)

Data are presented as mean (95% CI) adjusted for baseline values. ESWT: endurance shuttle walk test; RPE: rate of physical exertion; ISWT: incremental shuttle walk test; CRQ: Chronic Respiratory Disease Questionnaire; PPI: points per item; EE: energy expenditure; MET: metabolic equivalent. #: ESWT dyspnoea isotime score: comparison of dyspnoea scores at the end time of the shortest ESWT; ¶: ISWT dyspnoea isotime score: comparison of dyspnoea scores at the end time of the shortest ISWT; +: sedentary: awake time spent METs <1.5; §: light activity: time spent METs 1.5–<3; f: moderate activity: time spent METs 3–<6; ##: vigorous activity: time spent METs ⩾6. *: significant within-group difference from baseline; **: significant between-group difference.

Eur Respir J 2019; 53: 1802429

ORIGINAL ARTICLE
COPD

Oxygen compared to air during exercise training in COPD with exercise-induced desaturation

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In summary, this large randomised controlled trial with blinding of participants, trainers and assessors found that both Oxygen and Air groups significantly improved exercise capacity and HRQoL with no greater benefit from training with supplemental oxygen than with medical air. The clinical implication from this study is that supplemental oxygen to correct oxygen desaturation is not required for patients to benefit from exercise training. Thus, for people with COPD, who are normoxaemic at rest but who desaturate during exertion, exercise training programmes could be provided in venues where supplemental oxygen is not available, enabling pulmonary rehabilitation programmes to be more widely accessible in the community.

Eur Respir J 2019; 53: 1802429

The Salzburg COPD Exercise and Oxygen (SCOPE) study

- The Salzburg COPD Exercise and Oxygen (SCOPE) study was performed to test whether exercise training with supplemental oxygen might lead to higher training intensity when compared with medical air, and therefore would result in greater improvements in peak work rate and muscle strength

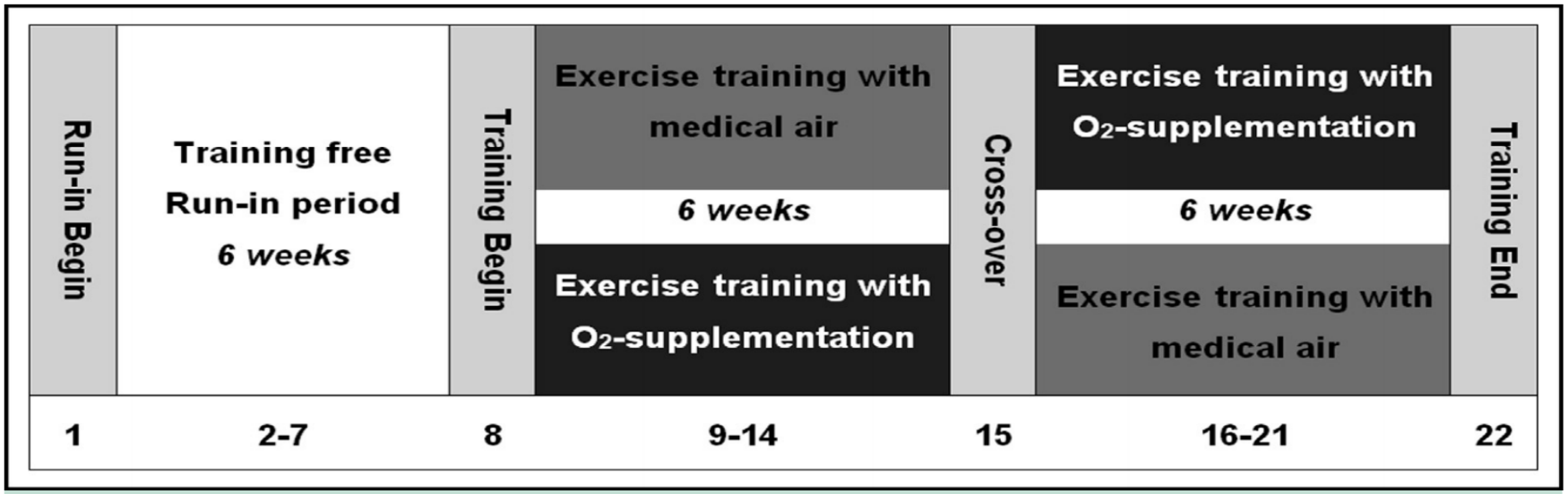
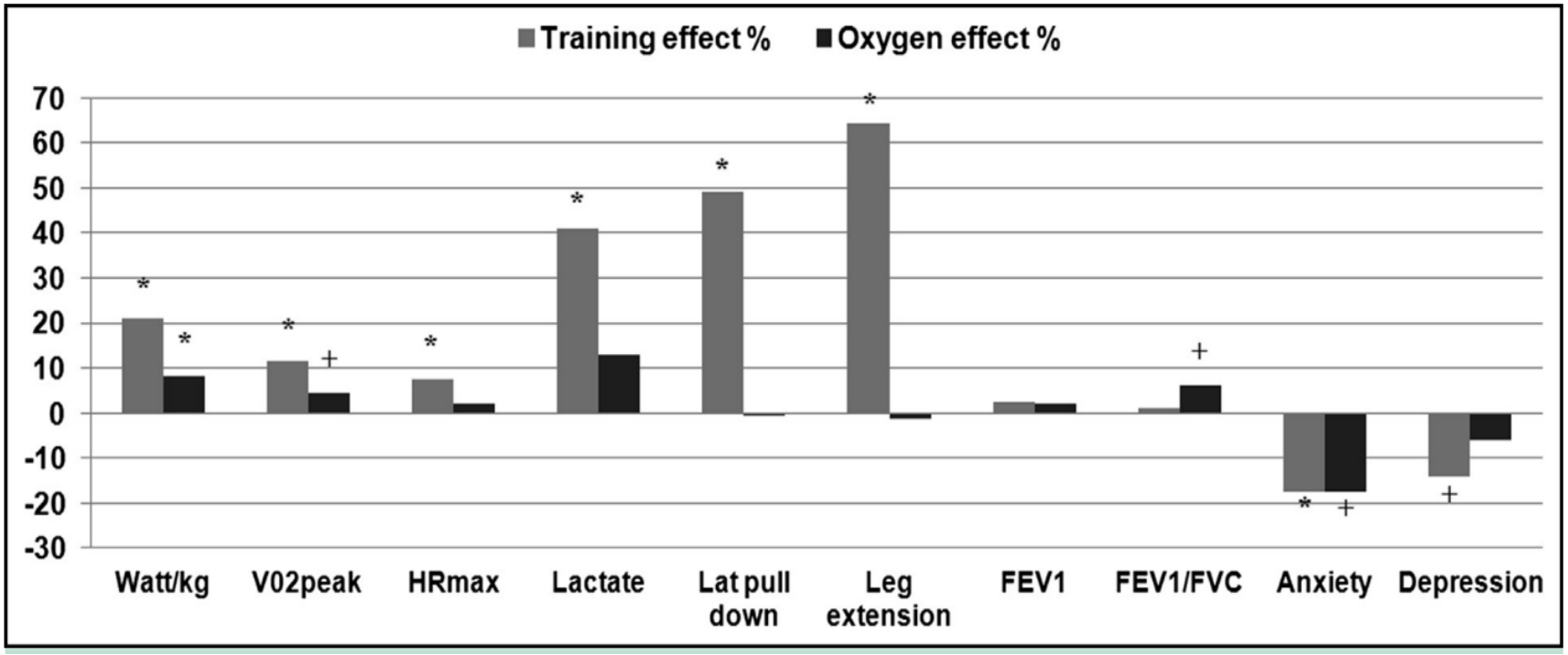


Figure 1 The SCOPE study design. A timeline (weeks) is shown at the bottom. All patients underwent a training-free run-in period lasting 6 weeks to optimize pharmacologic treatment according to international guidelines. Forty-four patients were randomized at training begin to group O_2-Air or group Air-O_2 and performed two 6-week periods of exercise training; patients started the training program with supplemental oxygen followed by medical air or vice versa. Study investigations were performed at run-in begin, training begin, crossover, and training end.

- Eligiblity criteria : stable COPD pt, FEV1 30~60%, resting PaO2>55mmHg and PCO2<45mmHg
- During endurance and strength training, as well as during additional gas-specific exercise testing, 10 L/min of oxygen (inspired oxygen fraction ~60%) or medical air was administered. For warmup and cooldown, gas supply was reduced to 4 L/min

SCOPE study. Am J Med 2016;129:1185-1193

The effect of supplemental oxygen in relation to the overall training effect



- The oxygen effect was defined as the difference between results achieved during exercise training with supplemental oxygen compared with medical air.
- Statistical significance is indicated by an asterisk (*), and trends (0.1> P > .05) are flagged by a plus sign (+).
- HRmax = maximal heart rate; lactate = at exhaustion; Lat pull down = latissimus pull down (10-repetition maximum strength test); leg extension = 10-repetition maximum strength test; VO2peak = peak oxygen uptake; Watt/kg = peak work rate.
- Anxiety and depression measured by the Hospital Anxiety and Depression Scale.

SCOPE study. Am J Med 2016;129:1185-1193

Effect of exercise with/without O2 on Exercise Capacity, Systemic Inflammation and Vascular Function

Table 2 Exercise Capacity, Systemic Inflammation and Vascular Function During the Study Period

	Run-In Start (Week 1) Mean (± SE)	Training Start (Week 8) Mean (± SE)	Training End (Week 22) Mean (± SE)	Training Effect %	Training Effect *P* Value	Exercise Training with Oxygen Delta (± SE)	Exercise Training with Medical Air Delta (± SE)	Oxygen Effect *P* Value
Exercise capacity								
Wpeak/kg, W/kg	1.11 (± 0.07)	1.10 (± 0.07)	1.33 (± 0.07)	20.91	< .001	0.16 (± 0.02)	0.07 (± 0.02)	.001
peak VO_2, mL/min/kg	19.04 (± 0.69)	18.43 (± 0.70)	20.57 (± 0.71)	11.61	< .001	1.50 (± 0.30)	0.65 (± 0.34)	.067
Inflammatory biomarkers								
Leptin 2-15 ng/mL	13.09 (± 2.47)	13.62 (± 2.44)	11.74 (± 2.29)	−13.80%	.043	−1.05 (± 0.85)	−0.83 (± 0.66)	.422
TNF-α <5 pg/mL	8.02 (± 0.39)	8.16 (± 0.54)	8.02 (± 0.58)	−1.72%	.412	−0.74 (± 1.02)	0.55 (± 0.95)	.249
IL-6 <7 pg/mL	7.91 (± 1.35)	5.03 (± 0.65)	4.88 (± 1.09)	−2.98%	.435	−0.01 (± 0.56)	−0.14 (± 0.72)	.443
hsCRP <0.1 mg/dL	0.69 (± 0.18)	0.56 (± 0.15)	0.57 (± 0.17)	1.79%	.486	−0.02 (± 0.14)	0.02 (± 0.20)	.445
Fibrinogen 160-400 mg/dL	431.86 (± 21.87)	423.17 (± 21.60)	388.24 (± 17.37)	−8.25%	.022	−29.83 (± 14.95)	−5.10 (± 18.59)	.204
Leucocytes 3.5-9.8 G/L	8.16 (± 0.39)	7.69 (± 0.37)	7.57 (± 0.37)	−1.56%	.315	0.23 (± 0.34)	−0.34 (± 0.30)	.176
Eosinophils % of Leucocytes <4%	2.79 (± 0.27)	3.32 (± 0.34)	3.19 (± 0.30)	−3.92%	.348	−0.30 (± 0.43)	0.17 (± 0.34)	.251
Eosinophils - absolute 0.00-0.45 G/L	0.22 (± 0.02)	0.25 (± 0.03)	0.24 (± 0.03)	−4%	.337	−0.01 (± 0.03)	0.00 (± 0.03)	.360
Endothelial function								
RHI	2.09 (± 0.18)	1.97 (± 0.12)	2.01 (± 0.12)	2.03%	.329	−0.14 (± 0.12)	0.18 (± 0.13)	.093
FRHI	0.49 (± 0.10)	0.47 (± 0.09)	0.45 (± 0.07)	−4.26%	.374	−0.04 (± 0.07)	0.02 (± 0.07)	.318
AI	18.65 (± 3.55)	19.23 (± 3.83)	22.47 (± 3.89)	16.85%	.105	0.23 (± 3.06)	3.02 (± 2.77)	.300
AI75	16.69 (± 2.69)	16.97 (± 3.26)*	19.37 (± 3.38)	14.14%	.156	0.12 (± 2.42)	2.29 (± 2.67)	.318
Endothelial progenitor cells								
EPCs early	0.000314 (± 0.000084)	0.000179 (± 0.000058)	0.000106 (± 0.000025)	−40.78%	0.129	0.000008 (± 0.000079)	−0.000082 (± 0.000065)	0.248
EPCs late	0.0487 (± 0.0167)	0.0751 (± 0.0305)	0.0197 (± 0.0057)	−73.77%	0.048	−0.0446 (± 0.0340)	−0.0236 (± 0.0113)	0.285

Table 2 shows the effect of exercise training and supplemental oxygen on main parameters of this study. For the presented study outcomes, significant carryover effects due to the crossover study design could be statistically excluded. Parameters that differed significantly between study groups at the start of training are indicated with an asterisk (*).

AI = Augmentation Index; AI75 = Augmentation Index corrected to a heart rate of 75 beats per minute; EPCs = endothelial progenitor cells; FRHI = Framingham RHI; hsCRP = high-sensitivity C-reactive protein; IL-6 = interleukin 6; peak VO_2: peak oxygen consumption; RHI = reactive hyperemia index; SE = standard error; TNF-α = tumor necrosis factor α; Wpeak = peak work rate.

SCOPE study. Am J Med 2021;134:e171-e180

Effect of exercise with/without O2 on Exercise Capacity, Systemic Inflammation and Vascular Function in patient with endothelial dysfunction

Table 3 Patients with Endothelial Dysfunction: Exercise Capacity, Systemic Inflammation and Vascular Function During the Study Period

	Run-In Start (Week 1) Mean (± SE)	Training Start (Week 8) Mean (± SE)	Training End (Week 22) Mean (± SE)	Training Effect %	Training Effect *P* Value	Exercise Training with Oxygen Delta (± SE)	Exercise Training with Medical Air Delta (± SE)	Oxygen Effect *P* Value
Exercise capacity								
Wpeak/kg, W/kg	1.05 (± 0.11)	1.06 (± 011)	1.28 (± 0.12)	20.75%	≤ .001	0.16 (± 0.02)	0.06 (± 0.02)	.002
peak VO_2, mL/min/kg	17.79 (± 1.06)	17.32 (± 1.00)	19.20 (± 0.92)	10.85%	.002	1.62 (± 0.47)	0.26 (± 0.37)	.030
Inflammatory biomarkers								
Leptin 2-15 ng/mL	18.30 (± 4.52)	18.08 (± 4.32)	15.61 (± 4.36)	−13.66%	.095	−0.49 (± 1.49)	−1.98 (± 1.08)	.226
TNF-α <5 pg/mL	8.24 (± 0.52)	8.78 (± 0.91)	7.70 (± 0.74)	−12.30%	.120	−2.52 (± 1.88)	1.44 (± 1.99)	.158
IL-6 <7 pg/mL	6.74 (± 1.63)	6.61 (± 1.18)	5.74 (± 2.24)	−13.16%	.315	−1.36 (± 0.59)	0.49 (± 1.53)	.121
hsCRP <0.1 mg/dL	0.41 (± 0.13)	0.71 (± 0.25)	0.68 (± 0.34)	−4.23%	.479	−0.27 (0.13)	0.25 (± 0.42)	.134
Fibrinogen 160-400 mg/dL	412.38 (± 25.02)	454.31 (± 40.66)	415.29 (± 26.17)	−8.59%	.122	−36.15 (± 27.47)	−0.62 (± 39.37)	.285
Leucocytes 3.5-9.8 G/L	8.11 (± 0.43)	7.79 (± 0.43)	7.57 (± 0.43)	−2.82%	.213	−0.21 (± 0.32)	0.00 (± 0.38)	.375
Eosinophil granulocytes <4%	2.96 (± 0.53)	3.67 (± 0.51)	3.03 (± 0.49)	−17.44%	.023	−0.37 (± 0.59)	−0.27 (± 0.46)	.461
Eosinophil granulocytes 0.00-0.45 G/L	0.23 (± 0.04)	0.28 (± 0.04)	0.23 (± 0.04)	−17.86%	.015	−0.03 (± 0.05)	−0.03 (± 0.04)	.492
Endothelial function								
RHI	1.59 (± 0.12)	1.43 (± 0.06)	1.74 (± 0.10)	21.68%	.001	0.06 (± 0.11)	0.25 (± 0.09)	.175
FRHI	0.15 (± 0.08)	0.06 (± 0.06)	0.29 (± 0.07)	383.33%	.002	0.05 (± 0.08)	0.17 (± 0.06)	.194
AI	12.05 (± 5.73)	10.27 (± 5.43)	17.98 (± 7.29)	75.07%	.022	2.67 (± 2.65)	5.04 (± 2.26)	.257
AI75	11.14 (± 4.44)	9.55 (± 4.22)	17.07 (± 6.05)	78.74%	.021	2.53 (± 2.15)	4.99 (± 2.89)	.268
Endothelial progenitor cells								
EPCs early	0.000396 (± 0.000151)	0.000250 (± 0.000120)	0.000101(± 0.000035)	−59.6%	.149	0.000055 (± 0.000173)	−0.000204 (± 0.000131)	.183
EPCs late	0.0465 (± 0.0213)	0.1080 (± 0.0579)	0.0189 (± 0.0094)	−82.5%	.085	−0.0602 (± 0.0614)	−0.0289 (± 0.0170)	.322

Table 3 shows the effect of exercise training and supplemental oxygen on main parameters of this study in a subgroup of subjects with endothelial dysfunction, defined as RHI <1.67, at the start of training. For the presented study outcomes, significant carryover effects due to the crossover study design could be statistically excluded.

AI = Augmentation Index; AI75 = Augmentation Index corrected to a heart rate of 75 beats per minute; EPCs = endothelial progenitor cells; FRHI = Framingham RHI; hsCRP = high-Ssensitivity C-reactive protein; IL-6 = interleukin 6; peak VO_2 = peak oxygen consumption, RHI = reactive hyperemia index; SE = standard error; TNF-α = tumor necrosis factor α; Wpeak = peak work rate.

SCOPE study. Am J Med 2021;134:e171-e180

Original research

Oxygen supplementation during exercise improves leg muscle fatigue in chronic fibrotic interstitial lung disease

Day1	• incremental cycling CPET on room air to peak

Day2	• constant-load CPET on compressed medical air
	  • at 60% of peak work rate determined during the incremental test
	  • Patients : cycled to symptom limitation ($Tlim_{air}$)
	  • Controls : were asked to interrupt the test at the same $Tlim_{air}$ of his/her matched patient

Day3	• constant-load CPET under supplemental O2
	  • patients : exercised again to $Tlim_{air}$ under supplemental O2
	  • Flow was titrated on an individual basis (FiO2=0.3-0.6) to ensure that resting SpO2 in the 98%-100% range and SpO2 ≥94% during exercise

Thorax 2020, Epub ahead of print.

Reversal of hypoxaemia with supplemental O2 led to a lower burden of leg discomfort, dyspnoea and fatigue

Table 3 Physiological and perceptual variables at rest and during constant work rate exercise in healthy controls and patients

	Controls	Patients					
	Air	Air	Supplemental O_2	Between-group difference (95% CI)	P value	Within-group difference (95% CI)	P value
Exercise							
Cardiovascular							
HR (beats/min)	107±13	119±21	109±22†	12 (-1 to 25)	0.057	−10 (−14 to −6)	<0.001
HR (% predicted)	73.0±9.9	80.8±11.4	73.8±12.6†	7.8 (-0.2 to 15.8)	0.055	−7.0 (-9.7 to −4.4)	<0.001
HR (% incremental)	81.2±5.9	98.0±7.6*	89.4±9.8†	16.9 (11.8 to 22.0)	<0.001	−8.6 (-11.8 to −5.4)	<0.001
Ventilatory							
VE (L/min)	38.5±6.8	49.4±6.8*	40.4±5.8†	10.9 (5.8 to 16.0)	<0.001	−9.0 (-11.3 to −6.7)	<0.001
VT (L)	1.66 (0.61)	1.32 (0.38)	1.20 (0.41]†	−0.26 (-0.46 to 0.04)	0.098	−0.13 (-0.19 to −0.06)	0.007
VT/IC	0.52±0.13	0.82±0.13*	0.77±0.14	0.29 (0.19 to 0.39)	<0.001	−0.05 (-0.10 to 0.00)	0.059
f (breaths/min)	26±4	39±9*	35±8†	13 (7 to 18)	<0.001	−4 (−6 to −2)	0.001
f/VT (L)	15 (14)	29 (19)*	28 (21)	14 (4 to 20)	0.002	0 (-2 to 2)	0.776
Gas exchange							
SpO_2 (%)	98 (2)	81 (9)*	98 (1)†	−17 (−20 to −14)	<0.001	17 (14 to 23)	<0.001
$PETCO_2$ (mm Hg)	36±2	33±5	38±5†	−2 (−5 to 1)	0.098	5 (3 to 6)	<0.001
Symptoms							
Dyspnoea	2.0 (3.0)	4.0 (3.0]*	3.0 (1.0]†	3.0 (2.0 to 4.0)	<0.001	−1.5 (-2.5 to −1.0)	0.002
Leg discomfort	3.0 (2.0)	4.0 (1.0]*	3.0 (1.0]†	2.0 (1.0 to 3.0)	0.005	−1.0 (-2.0 to −0.5)	0.005
Fatigue	3.0 (5.0)	6.0 (2.0]*	4.0 (2.0]†	3.0 (2.0 to 5.0)	0.001	−2.5 (-3.5 to −1.5)	0.002

Thorax 2020, Epub ahead of print.

Supplemental O2 significantly improved ΔTw in comparison to medical air

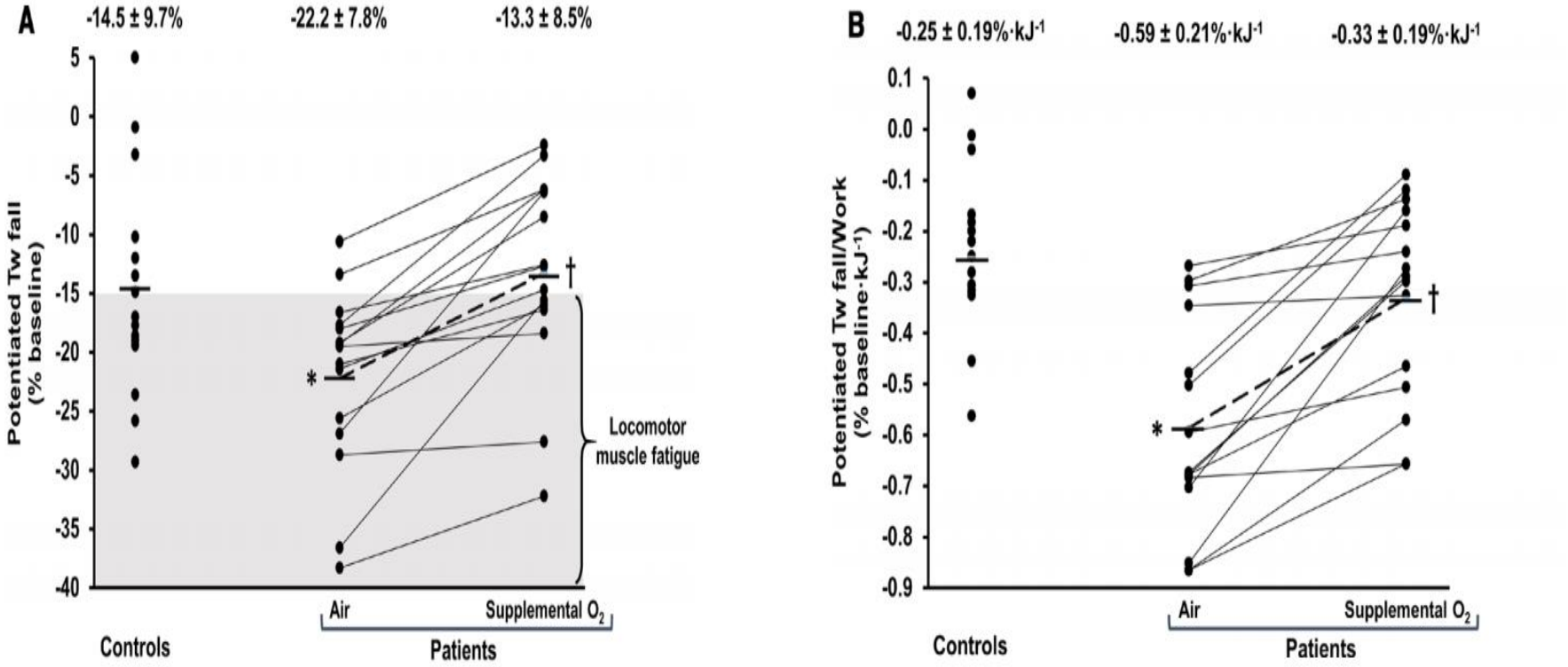


Figure 3 Locomotor muscle fatigue assessed by magnetic nerve stimulation in healthy controls and patients with fibrotic interstitial lung disease following constant work rate cycling under medical air or O_2 supplementation. *P<0.05: patients versus controls; †p<0.05: medical air versus O_2 supplementation in patients. Circles and thick bars indicate individual data and mean group values, respectively. *f*-ILD, fibrotic interstitial lung disease; O_2, oxygen; Tw, twitch.

Thorax 2020, Epub ahead of print.

Original research

Oxygen supplementation during exercise improves leg muscle fatigue in chronic fibrotic interstitial lung disease

Conclusion O_2 supplementation during exercise improves leg muscle oxygenation and fatigue in *f*-ILD. Lessening peripheral muscle fatigue to enhance exercise tolerance is a neglected therapeutic target that deserves clinical attention in this patient population.

Thorax 2020, Epub ahead of print.

Oxygen in pulmonary rehabilitation

	Statement or Recommendation
ATS/ERS (2013)	• The evidence to date does not appear to provide unequivocal support for the widespread use of oxygen supplementation during exercise training for all individuals with COPD, apart from those already receiving long-term oxygen therapy.
BTS (2013)	• Supplemental oxygen should not be routinely used for all patients undergoing pulmonary rehabilitation. (Grade B) • Supplemental oxygen during pulmonary rehabilitation should be offered to those who fulfil the assessment criteria for long-term or ambulatory oxygen unless there are compelling clinical reasons to use alternative criteria. (Grade D)
Thoracic Society of Australia and New Zealand (2017)	• Further research of oxygen supplementation during training is required in patients with COPD who have exercise-induced desaturation to reduce the uncertainty around its lack of effect to date (‘in research’ recommendation).
KATRD review (2020)	• Has not shown an advantage over compressed air when administered during rehabilitative exercise • May not always be necessary during rehabilitation • the ability to prevent desaturation and to enable the patient to exercise at a higher intensity is clearly advantageous

Am J Respir Crit Care Med 2013;188:e13-e64
Thorax 2013; 68: Suppl. 2, ii1-ii30
Respirology 2017; 22: 800-819
Tuberc Respir Dis 2020;83:257-267

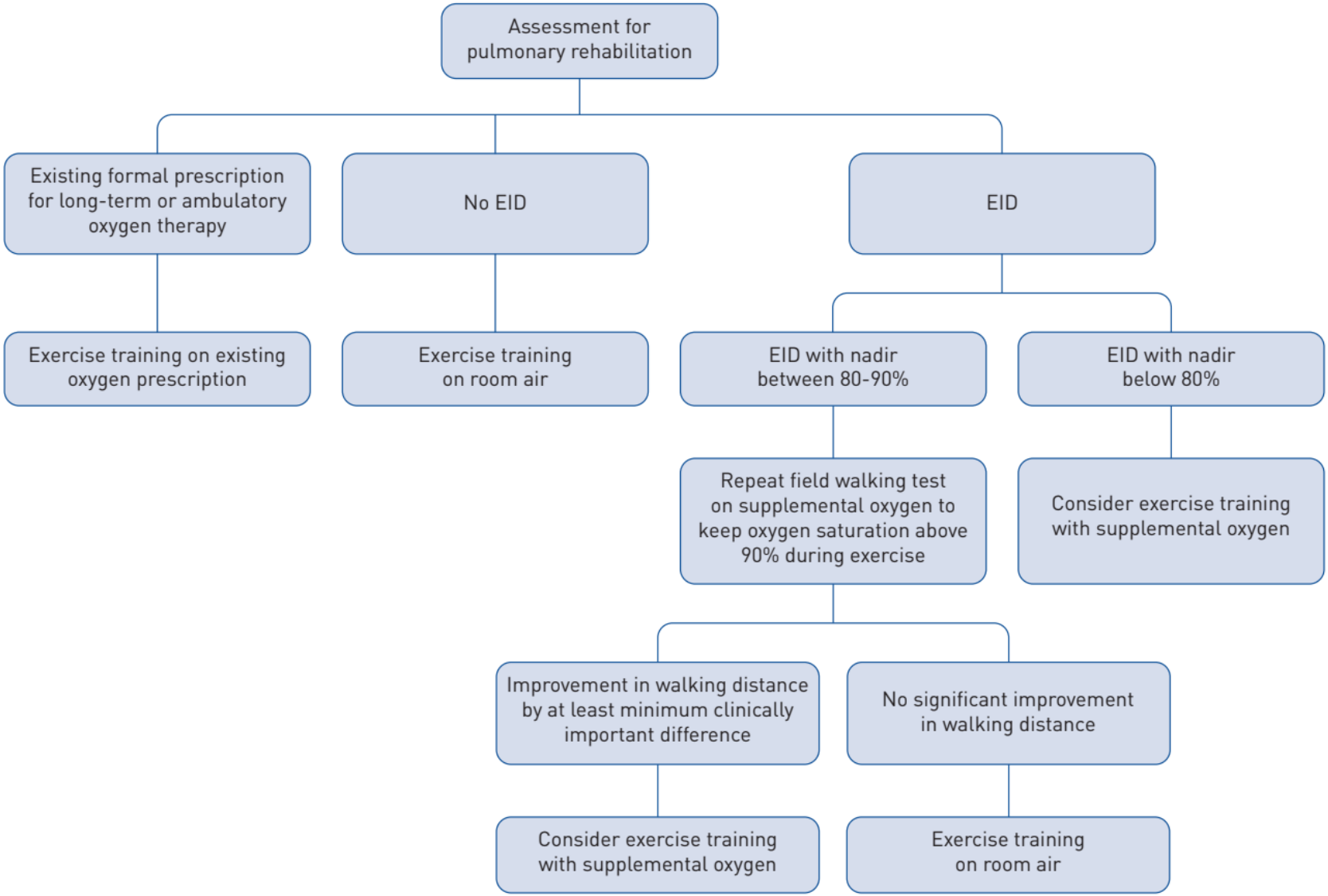


FIGURE 1 An algorithm to assess exercise induced oxygen desaturation (EID) (defined as nadir oxygen saturation below 90% during a field walking test performed on room air) in patients with chronic obstructive pulmonary disease referred for pulmonary rehabilitation.

ORIGINAL RESEARCH

Patient Perceptions of the Adequacy of Supplemental Oxygen Therapy

Results of the American Thoracic Society Nursing Assembly Oxygen Working Group Survey

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Ann Am Thorac Soc_2018;188:24-32

Sociodemographic characteristics, health utilization, and oxygen requirement (n = 1,926)

Characteristic	Total Sample (%)	Reported Problems (%)		
		Yes	No	*P* Value
Age, mean (SD), yr	64 (11)	63 (11)	65 (11)	<0.001
Female, %	72	54	46	0.001
Diagnosis, %				<0.001
COPD	39	44	56	
Interstitial lung disease	27	51	49	
Pulmonary hypertension	18	61	39	
Alpha-1 antitrypsin deficiency	8	60	40	
Lymphangioleiomyomatosis	4	70	30	
Other	5	55	45	
Employment, %				0.006
Retired	47	47	53	
Disabled	41	57	43	
Working full time	8	51	49	
Working part time	4	45	55	
Residence, %				0.04
Suburban	51	54	46	
Rural	28	46	54	
Urban	21	51	49	
Live in Competitive Bidding Area, %				0.02
Yes	44	55	45	
No	11	49	51	
Unsure	45	48	52	
Duration of oxygen use, %				<0.001
<1 yr	17	41	59	
1–5 yr	51	51	49	
>5 yr	32	57	43	
Oxygen requirement, %				
Continuous (24 h/d)	60	54	46	0.006
⩾5 L/min exertion (pulse or cont)	31	56	44	0.004
Health care utilization, %				
Hospital admission in past 12 mo	29	57	43	0.005
Emergency room visit in past 12 mo	34	56	44	0.006
Education, %				
Attended pulmonary rehab	63	53	47	0.17
Education on home oxygen				0.000
Oxygen delivery personnel	64	51	49	
Health care personnel	8	43	57	
None	10	64	36	
mMRC dyspnea score, mean (SD)				
Using oxygen	1.5 (1.2)	1.6 (1.2)	1.5 (1.2)	0.28
Not using oxygen	2.6 (1.2)	2.7 (1.2)	2.5 (1.2)	<0.001

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; mMRC = modified Medical Research Council.

*Because of missing data, the number of respondents varies for some items.

Ann Am Thorac Soc_2018;188:24-32

Portable O2 system used outside the home

Variable	Total Sample (%)	Reported Problems (%)		
		Yes	No	*P* Value
Type of portable oxygen system used				0.12
Portable oxygen concentrator	33	53	47	
Small compressed gas tanks	20	49	51	
Large "E" compressed gas tanks	16	52	48	
Liquid system	13	50	50	
Home fill system	13	62	38	
Length of time oxygen lasts away from home				0.060
About 1 h or less	11	59	41	
Up to 2 h	38	56	44	
Up to 4 h	32	49	51	
4–6 h	15	52	48	
More than 6 h	4	49	51	
Current portable system limits activities outside home				<0.001
Not at all	13	39†	61†	
Sometimes	35	52	48	
Frequently	23	57	43	
All the time	21	59†	41†	
Out-of-pocket oxygen copayment				<0.001
$0	52	47†	53†	
$1–$50	31	53	47	
$51–$100	9	61†	39†	
$101–$200	5	66†	34†	
>$200	3	54	46	

*Because of missing data, the number of respondents varies for some items.
†Cell significantly different ($P < 0.05$) as determined by examination of residuals and subpartioning of χ^2 analysis.

- When leaving home, 44% used pulse settings and 26% used continuous flow, 16% switched between pulse and continuous, and 1% were unsure of their type of flow setting (13% did not use oxygen when leaving the house).

Ann Am Thorac Soc_2018;188:24-32

Actual vs. desired hours of portable oxygen

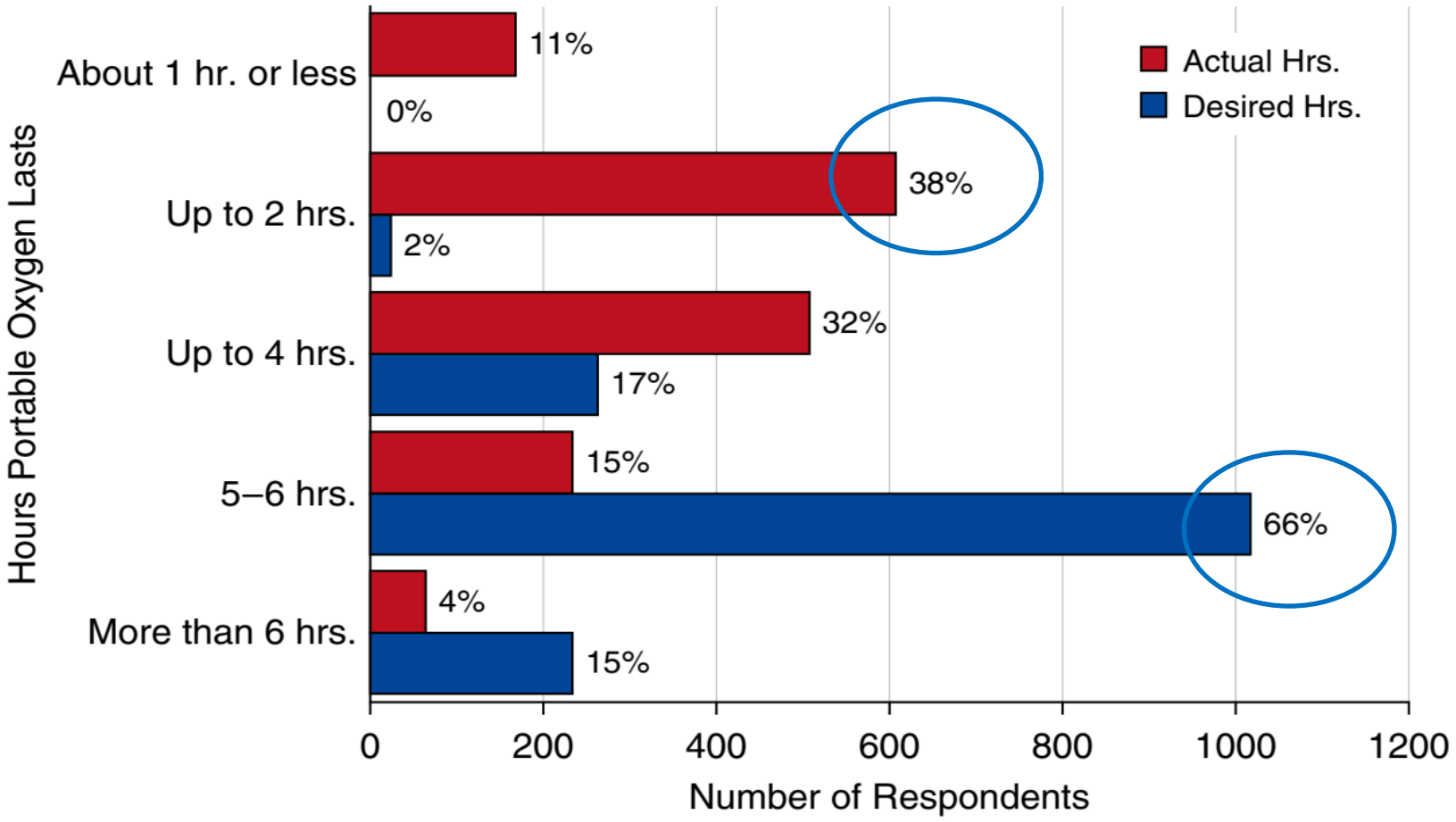

Figure 1. Actual versus desired hours that portable oxygen lasts.

Ann Am Thorac Soc 2018;188:24-32

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eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article

Respiratory Diseases

Check for updates

Current Situation of Home Oxygen Therapy for Chronic Obstructive Pulmonary Disease Patients in Korea

Joo Kyung Kim [1,2] Seung Hun Jang [1,2] Sunghoon Park [1,2] Joo-Hee Kim [1,2] Ji-Young Park [1,2] Kwang Ha Yoo [3] Young Sam Kim [4] Seong Yong Lim [5] and Yong Il Hwang [1,2]

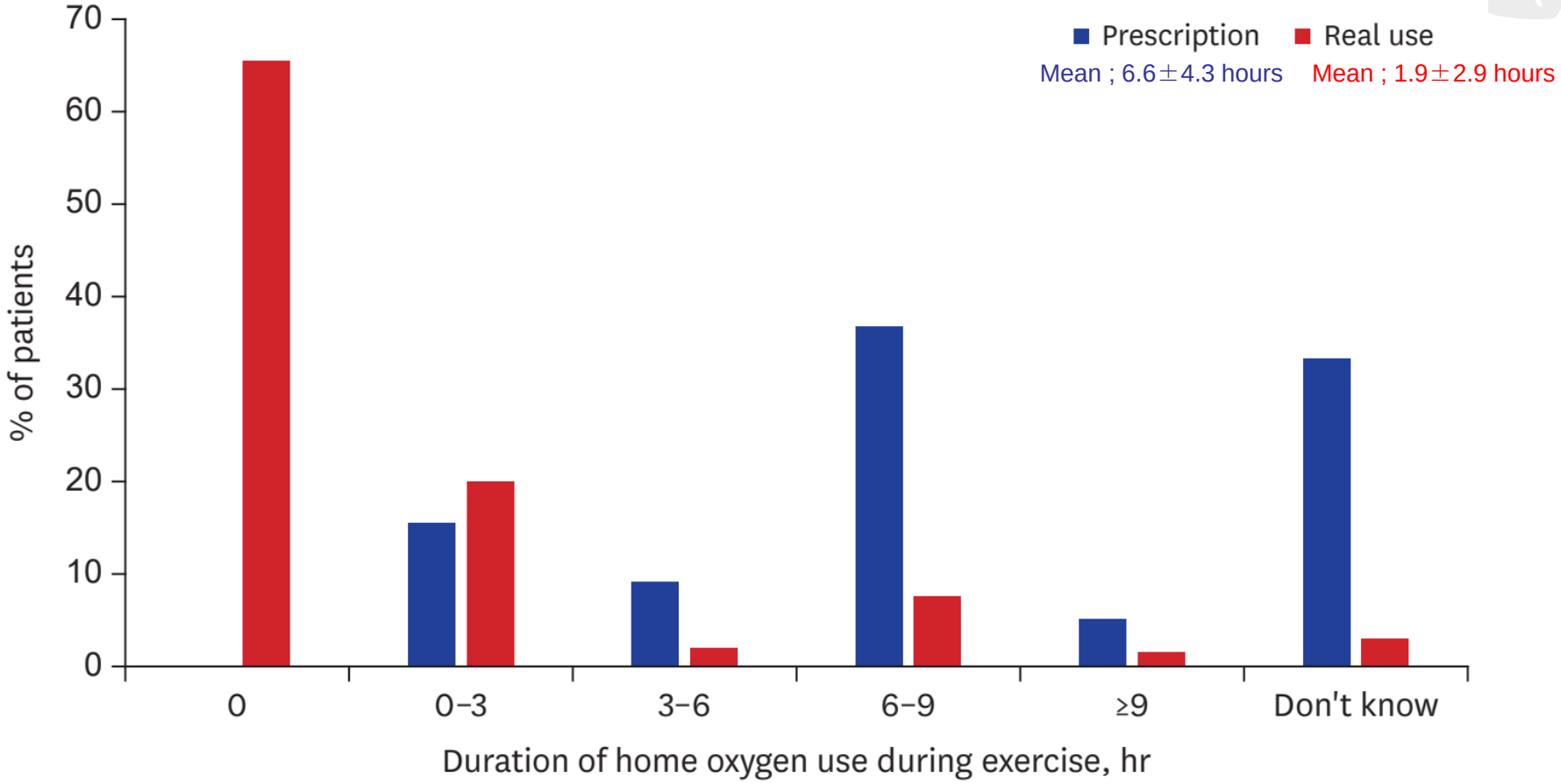
OPEN ACCESS

이동식 산소 치료 이용자 분포

단위 %

	전체	성별		연령대			
		남자	여자	60대 미만	60대	70대	80대 이상
	(n=195)	(n=149)	(n=46)	(n=18)	(n=50)	(n=78)	(n=49)
이용자	25.6	27.5	19.6	33.3	26	29.5	16.3
비이용자	74.4	72.5	80.4	66.7	74	70.5	83.7

Distribution of hours of oxygen use



J Korean Med Sci. 2020 Feb 3;35(4):e12

Oxygen prescription in specific conditions

	Patients with Hypoxemia*	Patients with Borderline hypoxemia**
Oxygen use restriction (yes)	13 (43.3)	17 (56.7)
When to restrict oxygen use?		
During sleep	4 (30.8)	
During exercise	6 (46.1)	13 (76.5)
Use only for dyspnea	1 (7.7)	4 (23.5)
High dose at exercise and low dose as usual	1 (7.7)	
No response	1 (7.7)	

Korean j Intern Med 2020, accepted

가정 산소치료 교육 자료 (Home Oxygen Therapy)

- 환자용 -

가정산소요법을 위한 산소노트

이 름: _____

대한결핵 및 호흡기학회

시범 사업 전후 가정산소치료 이용 실태

	시범 사업 전	시범 사업 후
안정 시 산소 사용 시간(시간)	15.6±8.21	11.2±6.40
안정 시 산소 사용 양(L)	2.08±1.63	1.81±0.58
운동 시 산소사용 시간(시간)	1.08±2.26	3.05±4.76
운동 시 산소 사용 양(L)	0.51±0.80	1.77±0.96
취침 시 산소 사용 시간(시간)	7.41±2.85	7.86±3.65
취침 시 산소 사용 양(L)	1.62±0.63	1.74±0.65

Manuscript in preparation

이동식 산소 사용

- 89.3% 사용
- 외출 시간 증가 : 55.2%

- 외출 시간 증가하지 않은 이유들
  - 무게가 무거워서
  - 평소에도 외출을 안하기 때문에
  - 충전 시간이 오래 걸려서
  - 냄새가 난다
  - 산소 유량이 맞지 않고 잘 안 나온다

Manuscript in preparation

Summary (1)

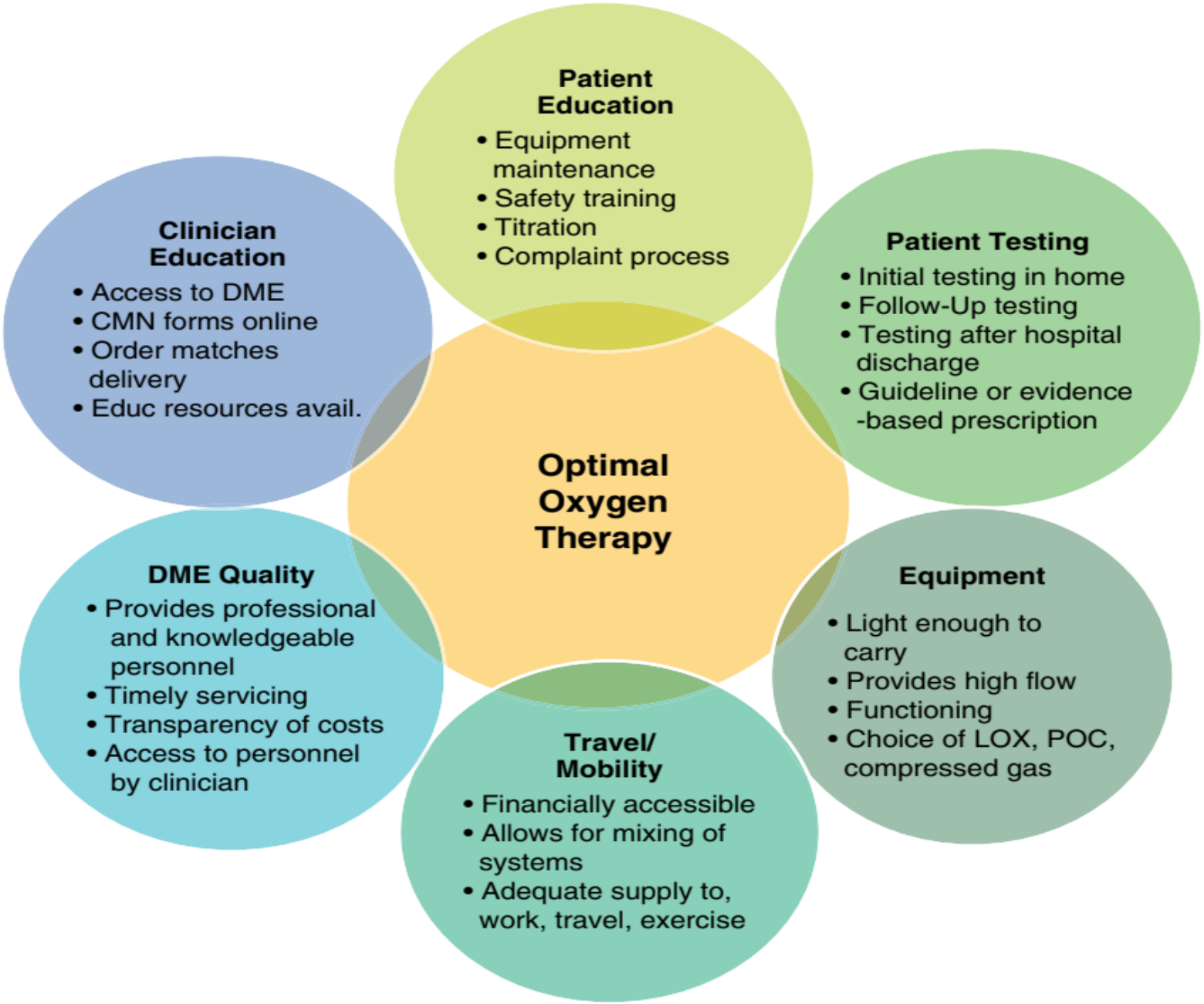
- Ambulatory oxygen acutely improves exercise capacity and may reduce breathlessness during exercise testing but there is little evidence regarding the effects of ambulatory oxygen when used in daily life in COPD patients.

Summary (2)

- The use of ambulatory oxygen in people with ILD seemed to be associated with short-term improved HRQL, but the medium- to long-term effects are unknown.
- Ambulatory oxygen may improve exercise capacity, but effects on physical activity in daily life have not been examined for ILD patients.

Summary (3)

- As there are scarce and inconclusive data to support the prescription of oxygen in patients who have normoxemia at rest but desaturate (sometimes markedly) with exertion.
- It needs to develop a stronger evidence base that will guide clinical practice for oxygen prescription



Ann Am Thorac Soc 2018;15:1369-1381

감사합니다

Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomised controlled trial

Dina Visca*, Letizia Mori*, Vicky Tsipouri, Sharon Fleming, Ashi Firouzi, Matteo Bonini, Matthew J Pavitt, Veronica Alfieri, Sara Canu, Martina Bonifazi, Cristina Boccabella, Angelo De Lauretis, Carmel J W Stock, Peter Saunders, Andrew Montgomery, Charlotte Hogben, Anna Stockford, Margaux Pittet, Jo Brown, Felix Chua, Peter M George, Philip L Molyneaux, Georgios A Margaritopoulos, Maria Kokosi, Vasileios Kouranos, Anne Marie Russell, Surinder S Birring, Alfredo Chetta, Toby M Maher, Paul Cullinan, Nicholas S Hopkinson, Winston Banya, Jennifer A Whitty, Huzaifa Adamali, Lisa G Spencer, Morag Farquhar, Piersante Sestini, Athol U Wells, Elisabetta A Renzoni

Lancet Respir Med 2018;6:759-70

Study design and participants

- a prospective, open-label, mixed-method, crossover randomised controlled trial done at three interstitial lung disease centres in UK
- Eligible patients
  - aged 18 years or older
  - Had fibrotic interstitial lung disease
  - Not hypoxic at rest (SaO2 ≥94% on room air)
  - Fall in SaO2 to 88% or less on a screening visit 6-min walk test (6MWT)
  - Stable respiratory symptoms in the previous 2 weeks
- Primary outcome
  - difference in HRQOL, measured with K-BILD after each 2-week treatment period between the oxygen and no-oxygen groups

K-BILD (King's Brief Interstitial Lung Disease Questionnaire)

- 15 questions, each with a seven-point response scale
- grouped into three domains: breathlessness and activities, chest symptoms, and psychological symptoms
- The individual domain and total scores can range from 0 to 100, with lower scores indicating worse quality of life.

Lancet Respir Med 2018;6:759-70

Trial flow

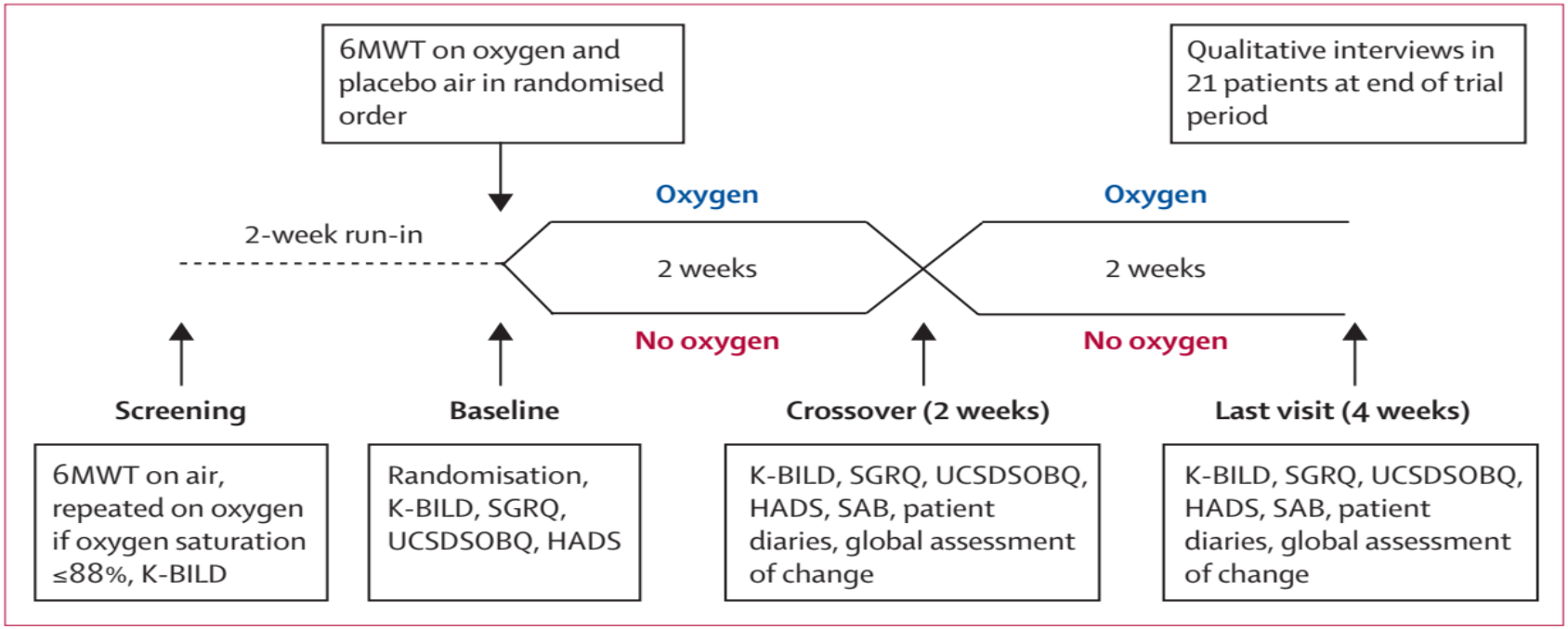


Figure 1: **Trial flow diagram**
6MWT=6-min walk test. K-BILD=King's Brief Interstitial Lung Disease questionnaire. SGRQ=St George's Respiratory Questionnaire. UCSDSOBQ=University of California, San Diego Shortness of Breath Questionnaire. HADS=Hospital Anxiety and Depression Scale. SAB=SenseWear Pro Armband.

- Participants were instructed to use the cylinders during routine activities of daily living.

Lancet Respir Med 2018;6:759-70

Baseline characteristics of randomly assigned patients

	Oxygen first (n=41)	No oxygen first (n=43)	Total (n=84)
Sex			
Male	26 (63%)	32 (74%)	58 (69%)
Female	15 (37%)	11 (26%)	26 (31%)
Age, years	68·9 (11·4)	66·8 (9·5)	67·9 (10·4)
Body-mass index	28·5 (5·1)	28·3 (4·6)	28·4 (4·8)
Former smoker	29 (71%)	24 (56%)	53 (63%)
Lung function			
Forced vital capacity, % predicted	71·1 (18·9)	75·1 (19·5)	73·1 (19·2)
FEV_1, % predicted	73·6 (21·0)	76·8 (19·4)	75·2 (20·2)
DLCO, % predicted	39·8 (10·2)	37·3 (8·2)	38·5 (9·3)
Composite physiological index	52·4 (9·1)	53·5 (7·7)	52·9 (8·4)
Screening 6-min walk test on air			
Distance, m	377·1 (122)	367·7 (104·7)	372·4 (113·0)
Peripheral transcutaneous oxygen saturation	84·4 (4·1)	85·7 (3·5)	85·1 (3·9)
Dilated right ventricle on echocardiogram*	6 (16%)	4 (10%)	10 (13%)

	Oxygen first (n=41)	No oxygen first (n=43)	Total (n=84)
Mean BNP (IQR), ng/L	38 (24–61)	29 (17–50)	34 (20–57)
Idiopathic pulmonary fibrosis	23 (56%)	26 (60%)	49 (58%)
K-BILD			
Total	51·2 (8·4)	49·7 (13·4)	50·5 (11·2)
Breathlessness and activities	33·8 (13·6)	34·9 (18·8)	34·4 (16·3)
Chest symptoms	57·4 (16·6)	55·3 (22·8)	56·3 (19·9)
Psychological symptoms	52·1 (10·8)	48·1 (16·7)	50·1 (14·1)
SGRQ			
Total	50·8 (15·1)	51·9 (18·1)	51·4 (16·6)
Symptoms	55·2 (21·9)	56·6 (21·4)	55·9 (21·5)
Activity	69·0 (16·3)	66·6 (19·2)	67·8 (17·8)
Impact	38·7 (18·1)	41·7 (20·6)	40·2 (19·3)
UCSDSOBQ	51·5 (21·2)	48·8 (24·5)	50·1 (22·8)
Hospital Anxiety and Depression Scale†			
Anxiety	9 (22%)	15 (35%)	24 (29%)
Depression	7 (17%)	13 (30%)	20 (24%)

Lancet Respir Med 2018;6:759-70

Outcomes

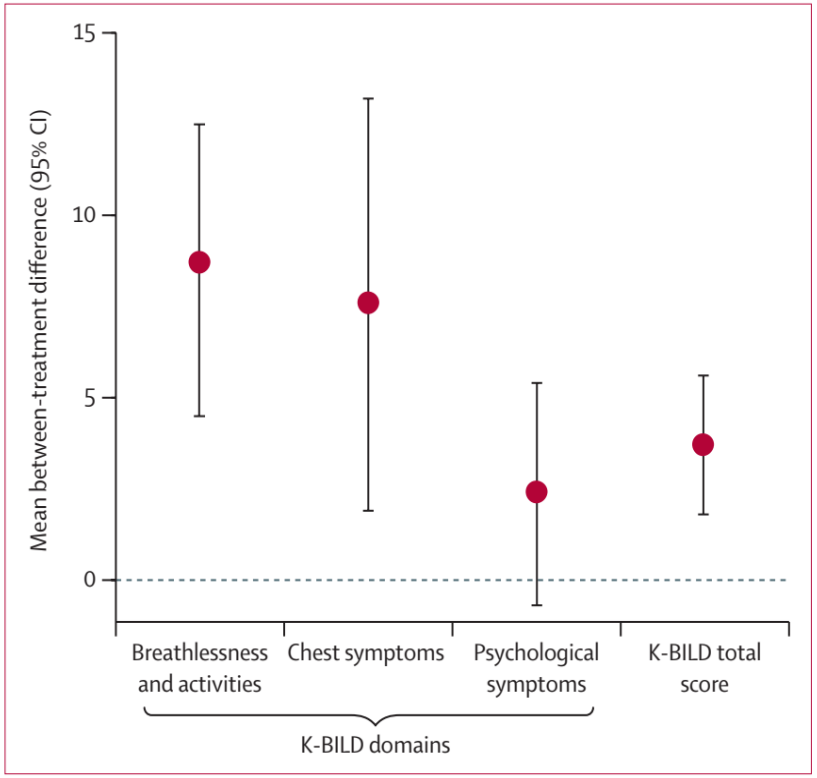


Figure 3: **Mean difference in K-BILD scores between ambulatory oxygen and no treatment, adjusted for order of treatment**
K-BILD=King's Brief Interstitial Lung Disease Questionnaire.

	Oxygen	No oxygen	Mean between-treatment difference (95% CI)	p value
K-BILD* (n=74)				
Total	55·5 (13·8)	51·8 (13·6)	3·7 (1·8 to 5·6)	<0·0001
Breathlessness and activities	44·4 (22·6)	35·8 (20·4)	8·6 (4·7 to 12·5)	<0·0001
Chest symptoms	65·5 (25·2)	57·9 (29·2)	7·6 (1·9 to 13·2)	0·009
Psychological symptoms	55·2 (19·6)	52·8 (19·6)	2·4 (–0·6 to 5·5)	0·12
UCSDSOBQ† (n=72)	41·0 (30·5)	49·1 (34·1)	–8·0 (–12·4 to –3·6)	<0·0001
SGRQ† (n=72)				
Total	48·7 (25·3)	52·4 (25·0)	–3·6 (–6·7 to –0·6)	0·018
Activity	61·5 (27·3)	68·9 (25·2)	–7·5 (–12·4 to –2·5)	0·003
Symptoms	53·3 (30·7)	54·9 (31·9)	–1·7 (–6·6 to 3·3)	0·51
Impact	39·7 (28·6)	41·8 (28·8)	–2·1 (–5·6 to 1·3)	0·22
Hospital Anxiety and Depression Scale‡ (n=70)				
Anxiety score ≥8	16 (23%)	18 (26%)	0·60 (0·14 to 2·50)§	0·47
Depression score ≥8	10 (14%)	18 (26%)	0·14 (0·02 to 1·16)§	0·14

Data are adjusted mean (SD) or n (%). K-BILD=King's Brief Interstitial Lung Disease Questionnaire. UCSDSOBQ=University of California, San Diego Shortness of Breath Questionnaire. SGRQ=St George's Respiratory Questionnaire. *Higher scores reflect better quality of life; minimal clinically important difference estimates for K-BILD scores are 4 (range 3·7–4·2) for total score, 6 (5·6–6·5) for breathlessness and activities score, 5·4 (4·6–6·9) for psychological symptoms score, and 0·5 (SD 8·9) for chest symptoms score.[34] †Lower scores reflect better quality of life. ‡Higher scores reflect higher depression and anxiety. §Data are odds ratio (95% CI), calculated on the basis of conditional logistic regression.

Table 3: **Quality-of-life, shortness-of-breath, and anxiety and depression scores after 2 weeks on and 2 weeks off ambulatory oxygen**

Lancet Respir Med 2018; 6: 759–70

Reduced breathlessness and improved walking ability after 2 weeks of ambulatory O2

Figure 4: **Numbers of patients reporting improved, same, or worse breathlessness (A) and walking ability (B) after 2 weeks on ambulatory oxygen or no treatment**

The wording of the questions is provided in the appendix (p 3).

Lancet Respir Med 2018; 6: 759–70

Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomised controlled trial

Interpretation Ambulatory oxygen seemed to be associated with improved HRQOL in patients with interstitial lung disease with isolated exertional hypoxia and could be an effective intervention in this patient group, who have few therapeutic options. However, further studies are needed to confirm this finding.

Lancet Respir Med 2018;6:759-70

Effect of training on peak response in incremental exercise and end-exercise responses to constant exercise

TABLE 2. EFFECT OF TRAINING ON THE PEAK RESPONSES IN INCREMENTAL EXERCISE TESTS IN WHICH AIR WAS RESPIRED

	Oxygen-training Group		Air-training Group	
	Before Training	After Training	Before Training	After Training
Work rate, W	54 (25)	67 (24)*	54 (27)	64 (29)*
SBP, torr	197 (23)	188 (26)*	187 (25)	187 (31)
DBP, torr	94 (10)	92 (8)*	92 (14)	87 (12)
Heart rate, beats/min	125 (22)	128 (22)	125 (16)	130 (19)
$\dot{V}O_2$, L/min	0.89 (0.22)	0.93 (0.27)	0.91 (0.36)	0.97 (0.32)
VCO_2, L/min	0.90 (0.28)	0.95 (0.30)	0.90 (0.39)	0.98 (0.32)
$\dot{V}E$, L/min	34 (8)	39 (10)*	36 (11)	39 (11)*
VT, L	1.06 (0.21)	1.21 (0.32)	1.11 (0.30)	1.18 (0.36)
f, breaths/min	30.9 (4.1)	32.6 (5.0)	32.2 (7.3)	33.8 (10.0)
Breathlessness	6.3 (2.5)	6.7 (2.1)	5.8 (1.8)	5.9 (1.5)
Leg fatigue	5.4 (2.4)	4.6 (2.7)	5.3 (2.2)	4.0 (2.4)
Lactate, mmol/L	4.2 (2.8)	4.8 (2.3)	3.8 (1.8)	4.6 (2.2)
Sa_{O_2}, %	94 (3)	93 (4)	93 (4)	93 (3)

Definition of abbreviations: DBP = diastolic blood pressure; f = respiratory rate; SBP = systolic blood pressure; $\dot{V}E$ = ventilation; $\dot{V}O_2$ = O_2 uptake.

Breathlessness and leg fatigue are measured on Borg scales (0–10), with higher scores denoting more severe symptoms. Values are mean ± SD.

*$p < 0.05$ pre–post training.

TABLE 3. EFFECT OF TRAINING ON THE END-EXERCISE RESPONSES TO CONSTANT WORK RATE EXERCISE IN WHICH AIR WAS RESPIRED

	Oxygen-training Group		Air-training Group	
	Before Training	After Training	Before Training	After Training
Work rate, W	40 (18)		41 (19)	
Time, min	6.6 (3.0)	21.4 (10.1)*	5.8 (2.4)	16.7 (8.0)*
SBP, torr	197 (24)	179 (25)*	182 (36)	187 (28)
DBP, torr	92 (9)	83 (12)	93 (19)	88 (18)
Heart rate, beats/min	122 (22)	120 (19)	125 (18)	120 (14)
$\dot{V}O_2$, L/min	0.89 (0.22)	0.84 (0.21)	0.93 (0.34)	0.93 (0.30)
VCO_2, L/min	0.86 (0.26)	0.81 (0.24)	0.90 (0.36)	0.88 (0.30)
$\dot{V}E$, L/min	33 (7)	34 (8)	33 (10)	34 (10)
VT, L	1.1 (0.3)	1.2 (0.3)	1.1 (0.3)	1.2 (0.3)
f, breaths/min	30.1 (3.9)	28.9 (3.3)	29.7 (7.0)	29.0 (5.6)
Breathlessness	7.9 (1.4)	5.3 (2.3)*	6.0 (2.0)	5.3 (2.5)
Leg fatigue	5.6 (2.3)	3.6 (2.4)	4.8 (2.5)	4.2 (2.7)
Sa_{O_2}, %	94 (3)	93 (4)	94 (3)	94 (2)

For definition of abbreviations, *see* Table 2.

*$p < 0.05$ pre–post training.

Values are means ± SD.

Am J Respir Crit Care Med 2003;168:1034-1042

Change in endurance shuttle walking test

Table 2. Change in endurance shuttle walking test with PR

	RA group	O_2 group	Difference	95% CI	*p* value
Mean change, seconds[a] (SD)	378 (364)	679 (317)	301	101–501	0.004
Mean change, m[b] (SD)	393 (395)	883 (484)	489	228–750	0.0005
Mean change, %[c] (SD)	77 (59)	204 (468)	127	31–223	0.01

PR: pulmonary rehabilitation; RA: room air.

[a] Change in exercise tolerance is expressed in seconds (the recommended method to report change in ESWT), allowing for differences in severity of disability.

[b] Change in exercise tolerance is expressed in metres to demonstrate change in distance walked allowing for differences in severity of disability.

[c] Change in exercise tolerance is expressed in percentage change.

Chron Respir Dis 2012;9:83-91