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

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Outline

- Background
- PICO
- Critical appraisal
- CASP 隨機對照試驗檢核表

Background

Background

- **PR** improves symptoms, quality of life, and physical and emotional participation in everyday activities.
- During PR it is common practice to **supplement oxygen** during exercise training with the aim of **facilitating higher exercise intensity**.
- In patients with stable COPD and resting or exercise-induced moderate desaturation, long-term oxygen treatment should **not** be prescribed routinely.
- **Individual patient factors** must be considered when evaluating the patient's need for supplemental oxygen. *(GOLD, 2021)*

Background

- **Exercise-induced oxygen desaturation (SpO2 <90%)**
  - >47%
  - Training intensity ↓ or mandatory rests
- **Supplemental oxygen during an acute bout of exercise**
  - ↓ minute ventilation at equivalent work rates
  - delays the onset of dynamic hyperinflation & dyspnoea
  - ↑ exercise capacity in people with moderate to severe COPD

PICO

臨床問題	COPD個案進行肺部復健需要給氧嗎?

PICO

問題/研究族群 Problem/Patient	COPD who were normoxaemic at rest and desaturated during exercise
給予的措施 Intervention	supplemental oxygen during exercise training
對照組 Comparison	medical air (sham intervention)
結果 Outcome	➢ Primary outcome: 1.exercise capacity ; 2.QOL ➢ Secondary outcome: 1.peak exercise capacity ; 2. level of dyspnoea ; 3.physical activity

Critical appraisal

- Methods
- Results
- Discussion

Study design

Inclusion criteria	Exclusion criteria
◦ 1. Dx of COPD on spirometry ◦ 2. ≧10 pack-year smoking ◦ 3. medically stable (AE ≧ 4wks) ◦ 4. SPO_2 <90 % during the 6MWT (RA)	◦ 1.long-term oxygen therapy ◦ 2.PaO_2 : < 55 mmHg ◦ 3. $PaCO_2$: > 50 mmHg ◦ 4. participated in any supervised exercise training in the last 12 months ◦ 5. co-morbidities affecting exercise: severe cardiovascular, neurological or musculoskeletal conditions

Study design

- multi-centre
- RCT
- blinding of participants, therapists and assessors
- intention-to-treat analysis

N=1362
Assess for eligibility

N=111
Randomised

- 6MWT

1. ≦350M vs >350M
2. SPO_2 : 89-86 vs <86

N=58
Oxygen
5L/min

N=52
Oxygen
8-wk

N=42
Oxygen

N=53
Air (sham)
5L/min

N=45
Air
8-wk

N=36
Air

Screening period	Randomized treatment period	Follow up period
		6 months

- Frequency: 3 times/wk, 8-wk
- Intensity: 80% of 6MWT speed; 60% of peak work rate
- Time: 30-40min (20 min. treadmill + 10-20min. Cycle)
- Type: supervised treadmill & cycle
- RPE : 3 – 4 (moderated – somewhat severe)

Study design

Progression of training

Treadmill
- 3 sessions
- RPE< 3

20 min
- < 3 Km/hr : ↑ 0.25 Km/hr
- >3 Km/hr : ↑ 0.5 Km/hr

20 min
- 5 km/hr
- 1-2%, 4.5km/hr

Cycle
- 6 sessions
- RPE< 3

10 min
- ↑ 5 min~ max 20 min.

20 min
- ↑ 5 watts

Outcome measure

Primary outcome	
Exercise capacity	Endurance shuttle walk test (ESWT)
QOL	Chronic Respiratory Disease Questionnaire (CRQ)

Secondary outcome	
peak exercise capacity	Incremental shuttle walk test (ISWT)
level of dyspnoea	Dyspnoea-12 Questionnaire
physical activity	multi-sensor activity monitor

Statistical analysis

- **Sample size calculation**

➢ It was estimated that **110 participants** were needed to ensure that **88 participants** completed the study, allowing for a **20% loss** to follow-up.

➢ This sample size was sufficient to provide **80% power** to detect as significant, at the (two-sided) 5% level.

- Data were analysed using SPSS version 22 (IBM, Armonk, NY, USA) on an **intention-to-treat** basis.

Baseline characteristics

TABLE 1 Participant characteristics

	Oxygen group	Air group	Loss to follow-up at end-training
Subjects	58	53	14
Age years	69±7	69±8	65±8
Male/female	30/28	31/22	8/6
BMI kg·m^{-2}	27±6	29±7	29±8
Current smoker	2 (3)	4 (8)	0 (0)
Pulmonary function			
FEV_1 L	1.2±0.4	1.2±0.5	1.1±0.2
FEV_1 % pred	47±17	45±16	42±8
FVC L	2.9±1.0	2.9±0.9	2.8±0.7
FVC % pred	83±19	79±15	78±14
FEV_1/FVC %	42±11	43±14	41±9
RV/TLC %	55±9	54±10	54±7
D_{LCO} % pred	48±17	50±16	57±21
GOLD grade			
I	2 (3)	1 (2)	0 (0)
II	16 (28)	18 (34)	3 (21)
III	31 (53)	24 (45)	10 (71)
IV	9 (16)	10 (19)	1 (8)
Arterial blood gases (room air)			
pH	7.4±0.03	7.4±0.04	7.4±0.02
P_{aO_2} mmHg	70.5±10	73.9±12	73.0±7
P_{aCO_2} mmHg	37.8±5	37.5±4	40.8±5
S_{aO_2} %	94±4	94±2	94±2
S_{pO_2} nadir %	85±4	85±4	86±3

Baseline characteristics

TABLE 1 Participant characteristics

	Oxygen group	Air group	Loss to follow-up at end-training
6MWD m	401±108	402±97	414±100
CRQ-Dyspnoea average score baseline	3.2±1	2.9±1	3.2±1
Dyspnoea-12 score baseline	15±9	17±9	16±7
Comorbidities			
Hypertension	14 (24)	26 (49)	7 (50)
Cardiac (including previous surgery)	14 (24)	19 (36)	4 (29)
Diabetes	11 (19)	5 (9)	2 (14)
Bronchiectasis	2 (3)	5 (9)	2 (14)
Other respiratory history	4 (7)	8 (15)	1 (7)
Cancer history	8 (15)	4 (8)	2 (14)
Neurological	3 (5)	4 (8)	2 (14)
Psychological	2 (3)	8 (15)	2 (14)
Increased cholesterol	14 (24)	10 (19)	4 (29)
Musculoskeletal	19 (33)	19 (36)	4 (29)

Results

MCID: 156

MCID: 47.5

MCID: 0.5

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.

Results

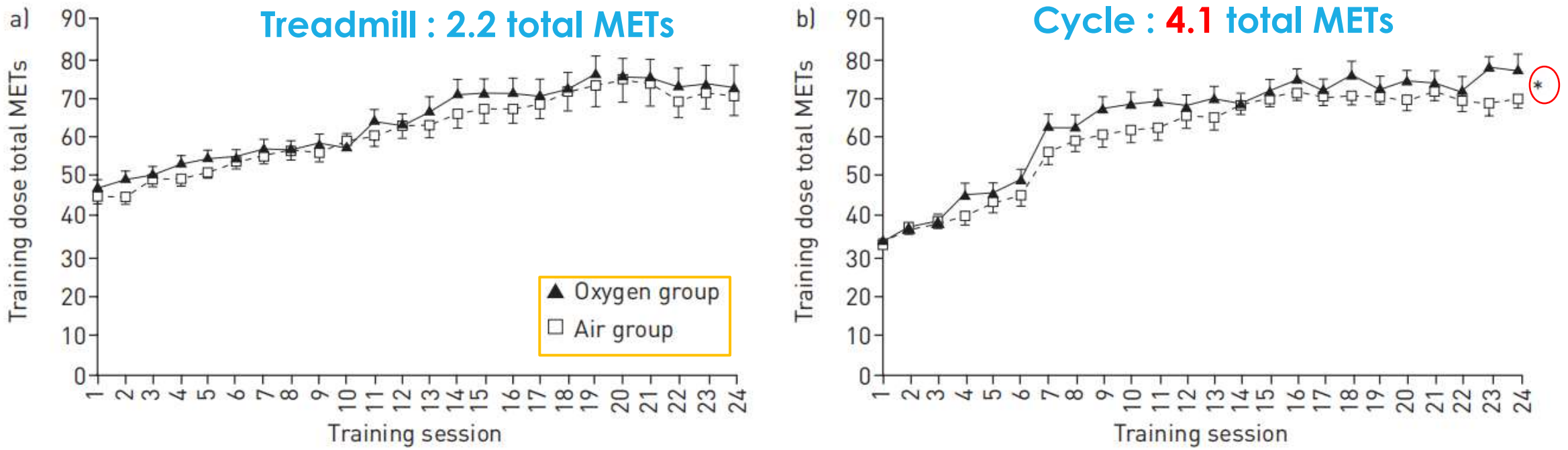

FIGURE 3 Training dose (duration×metabolic equivalents (METs)) per training session for a) treadmill exercise and b) cycle exercise in Oxygen and Air groups. Data are presented as mean±SE. *: $p<0.05$.

Results

TABLE 4 Oxygen saturation measured by pulse oximetry (S_{pO_2}) during treadmill and cycle exercise training

	Oxygen group	Air group	Between-group difference (Oxygen group–Air group)#
Treadmill S_{pO_2} %	94±3	89±4	5 (4–6)
Cycle S_{pO_2} %	94±3	92±3	3 (1–4)

Data are presented as mean±SD weekly measures of S_{pO_2} in all participants in the last 5 min of the 20-min treadmill and cycle exercise training, unless otherwise stated. #: mean (95% CI).

Adverse events

- The incidence and severity of adverse events were **similar** in both groups.

Oxygen group
One participant developed **atrial fibrillation** during a training session
One had a **syncopal** episode on the way to a training session
One death unrelated to the study
Air group
one participant had a **mild stroke** after finishing a treadmill training session
one participant had a minor heart attack on a nontraining day

Discussion

- **Supplemental oxygen** used during an 8-week supervised exercise training programme resulted in **no** greater improvements in endurance exercise capacity or HRQoL than did medical air in people with COPD who desaturated during a 6MWT.
- During treadmill training the Oxygen group was **not** able to achieve a greater training dose per session than the Air group.

	Oxygen group	Air group
Treadmill SpO_2 %	94±3	89±4
Cycle SpO_2 %	94±3	92±3

	Treadmill training		
	Oxygen Group Mean (SD)	Air Group Mean (SD)	Mean diff (95%CI)
Dyspnoea	3.2 (1.1)	3.7 (1.3)	0.58 (0.10 to 1.07)
RPE	3.1 (1.1)	3.9 (1.2)	0.81 (0.34 to 1.28)

Limitations

- acute response to oxygen supplementation was **not** evaluated
  - There may have been an imbalance between the groups of oxygen responders .
- As no baseline characteristics have been shown to **predict oxygen response**.
- The study was **not** powered to evaluate:
  - severe oxygen desaturation (i.e. SpO 2 ⩽80% during a 6MWT)
  - long-term oxygen therapy
  - other lung diseases (interstitial lung disease) or pulmonary hypertension.

CASP 隨機對照試驗檢核表

(A)研究結果可信嗎?

1. 研究問題是否清楚且聚焦?

考量點：一個聚焦的問題包括下列項目：

- ☐ 研究群體
- ☐ 介入措施
- ☐ 比較措施
- ☐ 研究的結果

是	V
不明確	
否	

問題/研究族群	COPD who were normoxaemic at rest and desaturated during exercise
給予的措施	supplemental oxygen during exercise training
對照組	medical air (sham intervention)
結果	➢ Primary outcome: 1.exercise capacity ; 2.QOL ➢ Secondary outcome: 1.peak exercise capacity ; 2. dyspnoea ; 3. PA

(A)研究結果可信嗎?

2. 受試者是否確實被隨機分派到不同組別?

考量點：

- ☐ 如何進行隨機分派?
- ☐ 研究者是否被隱匿分組訊息?

是	V
不明確	
否	

- Equal numbers of participants will be randomised to each group.
- Sequence generation will be determined using a computerised random number generator with stratification for study site, **6WMD** (≤350 metres vs >350 metres) and **level of nadir SpO2** from the 6MWT (nadir SpO2 between 89- 86 % vs < 86 %).

(A)研究結果可信嗎?

3. 受試者、健康相關工作人員及研究人員是否盲化？

考量點：

- ☐ 健康工作人員，如: 醫師、護理師等
- ☐ 研究人員，特別指結果評估者

是	V
不明確	
否	

- **Participants**, **exercise trainers** and **assessors** will be **blinded** as to whether the participants are receiving oxygen or medical air.
- **SPO2** was monitored during one training session each week by a **clinician independent** of the study and **blind** to group allocation.

(A)研究結果可信嗎?

4. 各組研究對象在一開始進入試驗時的基本特性是否相似?

考量點：

- 審視其他可能的影響因素，例如：年齡、性別、 社會階層等，這些也被稱為基準值的特質

是	V
不明確	
否	

- At baseline, both the Oxygen and Air groups were **similar** for **lung function**, **arterial blood gases** and **6MWD**.

(A)研究結果可信嗎?

5. 除了實驗的介入措施之外，各組的所有對待是否相同?

是	V
不明確	
否	

Exercise training

- Frequency: 3 times/wk, 8-wk
- Intensity: 80% of 6MWT speed; 60% of peak work rate
- Time: 30-40min (20 min. treadmill + 10-20min. Cycle)
- Type: supervised treadmill & cycle

(A)研究結果可信嗎?

6. 是否所有進入試驗的受試者在研究結論當中均被適當的考量過?

考量點：

- ☐ 試驗有提早結束嗎?
- ☐ 受試者是否一經隨機分派，均納入最後的分析?

是	V
不明確	
否	

- Participants who completed a **minimum of 16 training sessions** (66% of total sessions) were included in a **per-protocol analysis** using the same methods as the primary analysis.
- **intention-to-treat**

(B)研究結果為何?

7. 介入措施的效果有多大？

考量點：

- ☐ 測量那些結果?
- ☐ 主要結果是否有清楚界定?
- ☐ 每個研究結果有哪些發現?
- ☐ 是否有證據顯示有選擇性報告研究結果的情形?

是	V
不明確	
否	

Primary outcome	
1. Exercise capacity	Within-group(V) ; Between-group(-)
2. QOL	Within-group(V) ; Between-group(-)
Secondary outcome	
1. peak exercise capacity	Within-group(V) ; Between-group(-)
2. dyspnoea	Within-oxygen group(V) ; Between-group(-)
3. Physical activity	Within-group(-) ; Between-group(-)

(B)研究結果為何?

8. 介入措施的效果估計有多精確?

考量點：

- ☐ 信賴區間為何?
- ☐ 是否具有統計顯著性?

是	
不明確	V
否	

- This sample size was sufficient to provide **80% power** to detect as significant, at the (two-sided) 5% level.
- 研究結果組間是**沒有達統計學上的顯著差異**，在95%信賴區間上下值差異大於0.5

(C)研究結果對於當地病人有幫助嗎?

9. 研究結果是否可以應用在你的情境當中(或當地族群?)?

考量點：

- ☐ 你有理由相信你照顧的對象跟研究的受試者不同嗎?是否具有統計顯著性?
- ☐ 如果是的話，在哪些方面不同?

是	V
不明確	
否	

- Participants, on average, had severe COPD (mean± SD FEV1 46±17% predicted and FEV1/FVC ratio 0.43±0.13)

(C)研究結果對於當地病人有幫助嗎?

10. 是否臨床上重要的結果均已被考量？

考量點：

- ☐ 你希望看到其他有關結果的訊息嗎?
- ☐ 這篇試驗的需求有被清楚描述嗎?

是	V
不明確	
否	

- Exercise capacity
- QOL
- peak exercise capacity
- dyspnoea

(C)研究結果對於當地病人有幫助嗎?

11. 介入措施所帶來的效益是否值得付出傷害及成本的代價?

考量點：

- 即使這一點文章內沒有提到，你的看法呢?

是	V
不明確	
否	

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Air group

one participant had a **mild stroke** after finishing a treadmill training session
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COPD個案進行肺部復健時
血氧飽和濃度降低(80-88%)需要給氧嗎?

同意(綠牌)：18位

不同意(紅牌)：0位

需要更多文獻支持(黃牌)：10位