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# Which patients with moderate hypoxemia benefit from long-term oxygen therapy? Ways forward

Magnus Ekström<sup>1</sup>  
Thomas Ringbaek<sup>2</sup>

<sup>1</sup>Department of Respiratory Medicine and Allergology, Skåne University Hospital, Lund University, Lund, Sweden; <sup>2</sup>Respiratory Department, Hvidovre Hospital, Copenhagen, Denmark

**Abstract:** Long-term oxygen therapy (LTOT) improves prognosis in patients with COPD and chronic severe hypoxemia. The efficacy in moderate hypoxemia (tension of arterial oxygen; on air, 7.4–8.0 kPa) was questioned by a recent large trial. We reviewed the evidence to date (five randomized trials; 1,191 participants, all with COPD). Based on the current evidence, the survival time may be improved in patients with moderate hypoxemia with secondary polycythemia or right-sided heart failure, but not in the absence of these signs. Clinically, LTOT is not indicated in moderate hypoxemia except in the few patients with polycythemia or signs of right-sided heart failure, which may reflect more chronic and severe hypoxemia.

**Keywords:** survival, oxygen therapy, hypoxemia, COPD

## Introduction

Long-term oxygen therapy (LTOT) improved prognosis in patients with COPD and chronic severe hypoxemia in the NOTT and MRC randomized controlled trials (RCTs) conducted in the 1970s (n=290).<sup>1,2</sup> Based on the inclusion criteria of these trials,<sup>1,2</sup> the established indications for LTOT are chronic severe hypoxemia (tension of arterial oxygen [PaO<sub>2</sub>] on air ≤7.3 kPa) or moderate hypoxemia (7.4–8.0 kPa) with concurrent polycythemia (erythrocyte volume fraction [EVF] >0.54) or signs of right-sided heart failure or pulmonary hypertension.<sup>3</sup> Chronicity was defined as the resting daytime hypoxemia at least 3 weeks apart despite optimal therapy of the underlying disease(s) and the patient being in stable clinical condition.<sup>2</sup>

LTOT is given to prolong survival, and published evidence pertains to patients with COPD.<sup>4,5</sup> A recent Cochrane report found no evidence for benefit from LTOT on breathlessness or health-related quality of life in the absence of severe resting hypoxemia.<sup>6</sup> Surveys from several countries report that ~15%–45% of the patients on LTOT do not meet the hypoxemia criteria and that many patients on LTOT have moderate hypoxemia.<sup>7</sup> The effect of LTOT on mortality in moderate hypoxemia has been questioned,<sup>4,8</sup> most recently by the large Long-Term Oxygen Therapy Trial (LOTT; n=738).<sup>5</sup> We aimed to evaluate the effect of LTOT on mortality to inform its clinical usefulness and research priorities in patients with COPD and moderate hypoxemia. We also aimed to identify trial characteristics that could explain the differences in outcomes between studies with focus on the required level and chronicity of hypoxemia.

## Methods

We identified studies fulfilling all the inclusion criteria: RCT design; compared LTOT, defined as oxygen therapy prescribed ≥15 h/day, with air or no LTOT; included

Correspondence: Magnus Ekström  
Department of Medicine, Blekinge Hospital, SE-371 Karlskrona, Sweden  
Tel +46 455 731 000  
Email pmekstrom@gmail.com

patients with COPD and moderate hypoxemia; and reported outcome data on mortality. Trials were identified by searching Medline using keywords (“oxygen therapy” or “LTOT”), reference lists of published Cochrane reports,<sup>4,6</sup> recent clinical guidelines,<sup>3</sup> and papers in the field<sup>5</sup> up to May 19, 2017. Abstracts were screened against the eligibility criteria by Magnus Ekström. Data from full-text articles were extracted and cross-validated by both authors independently. Extracted data included study design, publication year, eligibility criteria, number of participants with moderate hypoxemia, study interventions, blinding, and findings. Disagreements were solved through consensus, and data were tabulated. Focus was on relating the difference in outcomes between studies to eligibility criteria including the required level and chronicity of hypoxemia. Meta-analysis was not performed due to heterogeneity in study designs and insufficient reported outcome data for people with moderate hypoxemia.

## Results

After screening 9,075 records, a total of five RCTs<sup>1,2,5,8,10</sup> (1,191 participants) of the efficacy of LTOT on mortality were included (Table 1). All participants had COPD, and the majority were men. Current smokers were included in the MRC trial (52% in the oxygen group and 33% in the control group) and in the NOTT (38% smoked regularly at the time of the study), whereas smoking was a contraindication for participation in the other three trials. None of the trials were blinded (Table 1). Moderate resting hypoxemia was defined as a PaO<sub>2</sub> (air) ≥7.4 kPa in all studies except LOTT where it was defined as a saturation using pulse oximetry (SpO<sub>2</sub>) of 89%–93%.

The number of participants with moderate hypoxemia was not separately reported in the NOTT and MRC trials. Moderate resting hypoxemia was present in all participants in the studies by Gorecka et al<sup>8</sup> (n=135) and Haidl et al<sup>10</sup> (n=28) and 419 of 738 participants (57%) in the LOTT.

LTOT prescribed 24 h/day decreased the mortality rate compared with oxygen only during the night in NOTT, and the effect was consistent between participants with PaO<sub>2</sub> (air) above or below 6.9 kPa. More specific outcomes for the group with moderate hypoxemia were not reported in NOTT or MRC. In the subsequent three trials<sup>1,2,5</sup> (n=582), there was no between-group difference in the mortality rate (Table 1).

In terms of eligibility criteria, participants were required to have stable hypoxemia across a defined time period in the NOTT (1 week), MRC (3 weeks), and in the trial by Gorecka et al (3 weeks). In the pilot study of Haidl et al,<sup>10</sup> patients were included in the trial during a COPD exacerbation. In the

**Table 1** Randomized trials on the effect of long-term oxygen therapy on mortality in patients with COPD and moderate hypoxemia

Study and year	Eligibility criteria	Number with moderate hypoxemia	Interventions	Blinding	Findings	Remarks
NOTT (1980) <sup>1</sup>	Inclusion criteria: age > 35 years; physician-diagnosed COPD (FEV <sub>1</sub> /FVC < 0.7 post-BD; TLC > 80% of predicted); PaO <sub>2</sub> ≤ 55 mmHg (7.3 kPa), or ≤ 59 (8.0 kPa) mmHg and one of: edema, EVF ≥ 0.55, or P pulmonale on ECG; stable at least two occasions > 1 week apart during a 3-week observation period. Exclusion criteria: LTOT ≥ 12/h previous 30 days; other significant diseases.	113 of 203 had a PaO <sub>2</sub> (air) > 6.9 kPa (52 mmHg). No other data on moderate hypoxemia reported.	LTOT (1–4 L/min) for 24 h/day vs 12 h/day. Actual use: 17.7 (SD, 4.8) vs 12.0 (SD, 2.5) h/day (self-report and flow-timers on equipment).	None	41% (nocturnal) vs 22% (continuous) died within 2 years, hazard ratio 1.94 (95% CI, 1.17–3.24). Average follow-up was 19.3 months. Consistent effect for patients with PaO <sub>2</sub> (air) under or above 6.9 kPa (52 mmHg).	Only 203 of 1,043 screened patients were included; 21% were excluded due to improved oxygenation. Participants had a mean age of 66 years; PaO <sub>2</sub> : 6.8 kPa (51 mmHg); PaCO <sub>2</sub> : 5.8 kPa (43.5 mmHg); EVF: 47%; and PAP: 30 mmHg (4.0 kPa). A total of 38% of the patients stated that they were smoking regularly at the time of the study.

MRC (1981) <sup>2</sup>	Inclusion criteria: age <70 years; chronic bronchitis or emphysema with FEV <sub>1</sub> <1.2 L; PaO <sub>2</sub> : 5.3–8.0 kPa (40–60 mmHg) stable in two measurements ≥3 weeks apart; and an “episode of heart failure with ankle edema”. Exclusion criterion: other significant diseases.	No specific information regarding the group with PaO <sub>2</sub> (air) 7.3–8 kPa out of the total 87 participants.	LTOT 2 L/min or higher (to achieve PaO <sub>2</sub> >60 mmHg [ $\geq$ 8.0 kPa]) given 15 h/day vs no treatment.	None	Number of deaths was 19/42 in the LTOT group and 30/45 in the control group. No difference in hospitalized days from exacerbations of respiratory failure. Adherence to LTOT was not measured. Participants were “urged to give up smoking”, but ~50% smokers (52% oxygen and 33% control group at the start, and 44% and 27% at the study end).	Mean age: 58 years; PaO <sub>2</sub> : 6.65 kPa (49.9 mmHg); PaCO <sub>2</sub> : 7.3 kPa (54.8 mmHg); EVF: 0.53; and PAP: 34 mmHg (4.5 kPa).
Gorecka et al (1997) <sup>8</sup>	PaO <sub>2</sub> : 7.4–8.7 kPa (56–65 mmHg) stable at least 3 weeks apart; age 40–80 years; COPD (FEV <sub>1</sub> /FVC <0.70 post BD); no other major disease.	135	LTOT $\geq$ 17 h/day by oxygen concentrator titrated to achieve PaO <sub>2</sub> >8.7 kPa (>65.3 mmHg) vs no treatment. Mean actual use in the oxygen group: 13.5 (SD, 4.4) h/day (measured by oxygen meter).	None	No effect on mortality. 23% died within 2 years (p=0.89). At least 3 years follow-up; average follow-up 40.9 (range: 2–85) months. 74 patients having a PaO <sub>2</sub> $\leq$ 8.0 kPa and 61 patients with a PaO <sub>2</sub> of >8 kPa. No differences in survival in these subgroups. No difference in survival in patients using oxygen for 15 or more hours/day compared with those less compliant (p=0.38).	Mean age 61.2 (SD, 8.5); PaO <sub>2</sub> (air) 8.0 (SD, 0.4) kPa; PaCO <sub>2</sub> (air) 5.9 (SD, 0.9) kPa; and EVF: 0.47 (SD, 0.06). All participants declared to be non-smokers at baseline.
Haidl et al (2004) <sup>10</sup>	COPD (FEV <sub>1</sub> /FVC <0.7); admitted for COPD exacerbation; PaCO <sub>2</sub> (air) >45 mmHg (>6.0 kPa) at rest or after exercise, reversed to <45 mmHg at discharge; PaO <sub>2</sub> (air) >55 mmHg (>7.3 kPa) at rest; mean nocturnal SpO <sub>2</sub> $\geq$ 90%. No malignant disease, left heart failure or other significant comorbidities.	28	Oxygen 2 L/min for >15 h/day vs no oxygen treatment. Mean actual use 10.4 h/day.	None	Increase in the endurance time and a decrease in the end-exercise dyspnea score in the LTOT group. Although not specified, the LTOT group was tested on oxygen (an acute effect of oxygen). No difference in survival.	No information on EVF or cor pulmonale.
LOTT (2016) <sup>5</sup>	SpO <sub>2</sub> 89%–93% at rest and/or moderate exercise-induced desaturation (during a 6MWT, SpO <sub>2</sub> $\geq$ 80% for $\geq$ 5 min and <90% for $\geq$ 10 s); COPD; age $\geq$ 40 years; no other disease that would affect oxygenation or survival.	419 (57%) of 738	Resting hypoxemia group: LTOT 2 L/min for 24 h/day vs no treatment. Exertional hypoxemia only group: at least 2 L/min to achieve SpO <sub>2</sub> >90% for $\geq$ 2/6 min during 6MWT, and 2 L/min during sleep.	None	133 (18%) had resting desaturation only, 319 (43%) had exercise-induced desaturation only, and 286 (39%) had both types of desaturation. Less than 10% died within 2 years. No effect on mortality, hospitalization, quality of life, or 6MWD. Median follow-up 18.4 months.	Mean age 69 years; no data on EVF, cor pulmonale or PaCO <sub>2</sub> .

**Abbreviations:** 6MWD, 6-min walk distance; 6MWT, 6-min walk test; BD, bronchodilation; CI, confidence interval; ECG, electrocardiogram; EVF, erythrocyte volume fraction; FEV<sub>1</sub>, forced expired volume in 1 s; FVC, forced vital capacity; LTOT, long-term oxygen therapy; PaCO<sub>2</sub>, tension of arterial carbon dioxide; PaO<sub>2</sub>, tension of arterial oxygen; PAP, pulmonary artery pressure; SpO<sub>2</sub>, saturation by pulse oximetry; TLC, total lung capacity.

LOTT, hypoxemia was assessed using pulse oximetry, not blood gases, and patients who had been hospitalized because of a COPD exacerbation or other acute conditions 30 days prior to screening were excluded. Signs of chronicity or more severe hypoxemia were required in people with moderate hypoxemia in the NOTT (edema, hematocrit  $\geq 55\%$ , or P pulmonale on ECG) and MRC trial (at least one episode of heart failure with ankle edema). Such signs of chronicity were not required in the three subsequent trials including the LOTT.

## Discussion

The current evidence supports that LTOT does not improve the prognosis in patients with COPD and moderate hypoxemia except in the few patients with polycythemia or signs of right-sided heart failure.

When considering the effect of LTOT, central factors are level of hypoxemia and its chronicity. The only trials showing a survival benefit of LTOT were the original NOTT and MRC trials that included patients with severe hypoxemia and patients with moderate hypoxemia together with signs of hypoxemia-related complications.<sup>1,2</sup>

It is also known that hypoxemia often is transient. About 30%–50% of hypoxemic patients initially classified as clinically stable did not fulfill the hypoxemia criteria at re-evaluation at 2–3 months.<sup>1,9</sup> Levi-Valensi et al<sup>9</sup> demonstrated that 20% of those who still met the hypoxemia criteria at 1 month were no longer hypoxemic after 3 months. Similar improvement may be seen in patients with moderate hypoxemia. After a 1–3 week re-evaluation period in the NOTT, only 203 (19%) of 1,043 screened patients were included, and 21% of exclusions were due to improved blood gases.<sup>1</sup> The re-evaluation of blood gases and, in patients with moderate hypoxemia, the requirement of signs of possible hypoxemia complications is likely to have restricted inclusion in the NOTT and MRC study mainly to patients with underlying chronic and severe hypoxemia. The lack of such measures, except in the study by Gorecka et al,<sup>8</sup> could partly explain the lack of effectiveness of LTOT in more recent trials that did not assess the chronicity of hypoxemia and highlight the importance of re-evaluating hypoxemia in clinical practice.<sup>5,10</sup>

Compared with patients in the NOTT and MRC trial, patients starting LTOT are now older and have more comorbidities,<sup>11,12</sup> as well as improved treatment of COPD and comorbid conditions such as cardiovascular diseases. In light of this and the reviewed evidence to date, we propose that the current hypoxemia criteria of LTOT should be

**Table 2** Effect of LTOT in relation to level of hypoxemia and signs of chronicity

Hypoxemia level	With signs of chronicity	Without signs of chronicity
Severe hypoxemia (PaO <sub>2</sub> $\leq 7.3$ kPa)	LTOT indicated	LTOT; trial <sup>a</sup>
Moderate hypoxemia (PaO <sub>2</sub> 7.4–8.0 kPa)	Unclear; trial <sup>b</sup>	LTOT not indicated

**Notes:** Signs of chronicity include secondary polycythemia (EVF  $>0.54$ ) or signs of right-sided heart failure or pulmonary hypertension. <sup>a</sup>LTOT may be provided based on the NOTT<sup>1</sup> and MRC<sup>2</sup> study. We suggest the need for an efficacy trial of LTOT in people with PaO<sub>2</sub>  $>7.0$  kPa without signs of chronicity. <sup>b</sup>Usefulness of LTOT was supported by NOTT but is questionable in light of the LOTT; an efficacy trial is needed.

**Abbreviations:** EVF, erythrocyte volume fraction; LTOT, long-term oxygen therapy; LOTT, Long-Term Oxygen Therapy Trial; PaO<sub>2</sub>, tension of arterial oxygen.

challenged (Table 2). Trials are needed on the efficacy of LTOT in people with: 1) moderate hypoxemia and signs of chronicity, based on the LOTT;<sup>1</sup> 2) PaO<sub>2</sub> 7.0–7.4 kPa, given the recent negative data in moderate hypoxemia, especially if trials in moderate hypoxemia and signs of chronicity turn out to be negative. Trials should establish and require chronicity of the hypoxemia and, in addition to survival, evaluate effects on hospitalizations, breathlessness, and quality of life where data are insufficient or lacking in severe hypoxemia.<sup>1,2</sup>

## Conclusion

There is no evidence that LTOT has beneficial effect on patients with moderate hypoxemia without signs of chronic hypoxemia, and more studies are needed to establish solid evidence-based criteria for LTOT.

## Author contributions

ME contributed to concept and design. Both authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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