

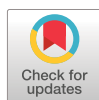


Oximetry neither to prescribe long-term oxygen therapy nor to screen for severe hypoxaemia

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Although transcutaneous pulse oximetry is widely used to diagnose severe hypoxaemia and prescribe long-term oxygen therapy in COPD, up to 40% of patients who qualify for this therapy would be denied treatment using the saturation threshold of $\leq 88\%$ <https://bit.ly/3jolWU5>

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Abstract

Background and objective Transcutaneous pulse oximetry saturation (S_{pO_2}) is widely used to diagnose severe hypoxaemia and to prescribe long-term oxygen therapy (LTOT) in COPD. This practice is not based on evidence. The primary objective of this study was to determine the accuracy (false positive and false negative rates) of oximetry for prescribing LTOT or for screening for severe hypoxaemia in patients with COPD.

Methods In a cross-sectional study, we correlated arterial oxygen saturation (S_{aO_2}) and S_{pO_2} in patients with COPD and moderate hypoxaemia ($n=240$) and calculated the false positive and false negative rates of S_{aO_2} at the threshold of $\leq 88\%$ to identify severe hypoxaemia (arterial oxygen tension (P_{aO_2}) ≤ 55 mmHg or $P_{aO_2} < 60$ mmHg) in 452 patients with COPD with moderate or severe hypoxaemia.

Results The correlation between S_{aO_2} and S_{pO_2} was only moderate (intra-class coefficient of correlation: 0.43; 95% confidence interval: 0.32–0.53). LTOT would be denied in 40% of truly hypoxaemic patients on the basis of a $S_{aO_2} > 88\%$ (*i.e.*, false negative result). Conversely, LTOT would be prescribed on the basis of a $S_{aO_2} \leq 88\%$ in 2% of patients who would not qualify for LTOT (*i.e.*, false positive result). Using a screening threshold of $\leq 92\%$, 5% of severely hypoxaemic patients would not be referred for further evaluation.

Conclusions Several patients who qualify for LTOT would be denied treatment using a prescription threshold of saturation $\leq 88\%$ or a screening threshold of $\leq 92\%$. Prescription of LTOT should be based on P_{aO_2} measurement.

Introduction

Two landmark trials conducted >40 years ago provided scientific evidence that long-term oxygen therapy (LTOT) may prolong life [1, 2]. These two trials targeted patients with COPD and severe daytime hypoxaemia documented by direct arterial blood gas (ABG) measurement. The inclusion criteria of both studies still serve as current indications for LTOT in COPD, with minor variations worldwide [3].

In several jurisdictions, LTOT is actually prescribed and reimbursed on the basis of the measurement of oxygen saturation by transcutaneous pulse oximetry (S_{pO_2}) alone. For instance, in the United States, clinicians may use either a partial pressure of oxygen in arterial blood (P_{aO_2}) ≤ 55 mmHg or a $S_{pO_2} \leq 88\%$ (or a P_{aO_2} of 56 to 59 mmHg, or S_{pO_2} of 89% with evidence of cor pulmonale or erythrocythaemia) at rest in establishing severe hypoxaemia [4]. The authors of the recently published American Thoracic Society clinical practice guidelines for home oxygen therapy in adults with chronic lung disease recognised the limitations of S_{pO_2} for oxygen prescription. Nevertheless, the panel supported its use to “improve the



usability of the guideline report in circumstances in which ABG measurements (are) not available” [5]. In Canada, the use of S_{pO_2} as a criterion for funding is inconsistent among provinces [6]. Although convenient, the practice of using pulse oximetry to determine the need for LTOT is not based on clinical evidence. The most recent British Thoracic Society guidelines for home oxygen use in adults suggested that pulse oximetry may be used for screening patients who might be candidates for LTOT. The guidelines recommend that patients with a resting stable saturation measured by transcutaneous pulse oximetry (S_{pO_2}) $\leq 92\%$ should be referred for ABG assessment in order to assess eligibility for LTOT [7]. A good practice is also to elevate this threshold to $\leq 94\%$ if end-organ damage (cor pulmonale or erythrocythaemia) is noted [7].

S_{aO_2} and P_{aO_2} are predictably related from the oxygen–haemoglobin dissociation curve. Although clinicians often use S_{pO_2} as a substitute for S_{aO_2} , several studies reported that S_{aO_2} and S_{pO_2} are only moderately correlated [8–10]. Consequently, S_{pO_2} may not be as reliable as measuring P_{aO_2} to establish the presence of hypoxaemia [11]. By using pulse oximetry alone for LTOT prescription, clinicians and patients should be aware of the potential for misclassification, that is denying LTOT in truly hypoxaemic patients on the basis of a $S_{pO_2} > 88\%$ (*i.e.*, false negative result), or prescribing LTOT on the basis of a $S_{pO_2} \leq 88\%$ in patients who would not qualify for LTOT if ABG were actually measured (*i.e.*, false positive result). Accordingly, our primary objectives were: 1) to demonstrate the correlation between S_{pO_2} and S_{aO_2} ; and 2) to determine the false positive and false negative rates of LTOT prescriptions in patients with COPD if it was based on S_{aO_2} alone. A secondary objective was to determine the S_{aO_2} thresholds at which the indication of LTOT can be ruled in or ruled out.

Material and methods

Design and patients

In a cross-sectional study, the results of ABG obtained from three separate groups of patients were analysed. First, we extracted the results of baseline ABGs of patients who participated in the International Nocturnal Oxygen (INOX) trial, a 4-year, multicentre, randomised, placebo-controlled trial of nocturnal oxygen therapy in patients with COPD [12]. To be included in the trial, patients had to have nocturnal oxygen desaturation without qualifying for LTOT. These patients usually have moderate hypoxaemia at rest (*i.e.*, P_{aO_2} approaching the threshold of LTOT prescription [13]). ABGs were available in 240 of 243 patients who were randomised in the INOX trial (Cohort 1). Arterial blood was drawn from patients in sitting position. As per protocol, S_{pO_2} was also measured within 1 hour of arterial blood sampling using PalmSAT 2500™ oximeter only (Nonin Medical Inc., Plymouth, MN, USA).

Second, we obtained from the respiratory home care programme of the Quebec City area (province of Quebec, Canada) the result of the ABG of patients registered in the programme as of January 1, 2015 with a main diagnosis of COPD who were prescribed LTOT (Cohort 2; $n=212$). To be admitted to the programme, severe hypoxaemia ($P_{aO_2} \leq 55$ mmHg or P_{aO_2} in the range of 56 to 59 mmHg with clinical evidence of cor pulmonale or erythrocythaemia [1]) must be strictly demonstrated in stable condition. Patients were not allowed in the programme on the basis of S_{pO_2} alone, so that S_{pO_2} was not recorded in this cohort.

We also retrieved from the laboratory of biochemistry of our institution the results of all consecutive ABGs measured between January 2009 and June 2017 in outpatients or inpatients while breathing room air (Cohort 3; $n=848$). ABG of patients in an intensive care unit or in the recovery room, or those receiving supplemental oxygen were therefore excluded. Each patient contributed only one sample of arterial blood. The underlying diagnoses and indication of ABG measurement were irrelevant to the objectives of this study.

Measurements

Modern blood gas analysers measure P_{aO_2} using an amperometric electrode and S_{aO_2} using spectrophotometry [14]. S_{aO_2} is obtained by dividing the concentration of oxyhaemoglobin by the sum of the concentrations of oxyhaemoglobin and deoxyhaemoglobin in the sample. Patients in Cohorts 1 and 2 came from several locations, and ABGs were analysed using different blood gas analysers across institutions. In Cohort 3, all ABGs were analysed on an ABL 800 Flex blood gas analyser (Radiometer, Copenhagen, Denmark). Patient temperature was not noted; in all measurements it was assumed to be 37°C.

Patient and public involvement

Patients were not directly involved in this study, which is a secondary analysis of data obtained from the INOX trial and a retrospective analysis of data kept in files at the respiratory home care programme of the

TABLE 1 Baseline characteristics

	Cohort 1: patients with COPD and isolated nocturnal desaturation	Cohort 2: patients with COPD and severe hypoxaemia	Cohort 3: unselected patients
Subjects n	240	212	848
Age years	69±8	72±10	72±12
Sex, male n (%)	157 (65%)	97 (46%)	460 (54%)
P_{aO_2} mmHg	67±7	52±5	57±10
S_{aO_2} %	93±2	87±4	89±5
S_{pO_2} %	93±2	N/A	N/A
P_{aCO_2} mmHg	42±6	47±8	44±8
pH	7.42±0.03	7.41±0.04	7.43±0.04

Data expressed as mean±SD unless otherwise stated. 1 mmHg=0.133 kPa; 1 kPa=7.50 mmHg. N/A: not available. P_{aO_2} : arterial oxygen tension; S_{aO_2} : arterial oxygen saturation; S_{pO_2} : pulse oximetry saturation; P_{aCO_2} : arterial carbon dioxide tension.

Quebec City area and at the laboratory of biochemistry of our institution. It received approval from the Research Ethics Committee of our institution (CER-IUCPQ-UL: 2021-3592, 22044).

Statistics

We used simple descriptive statistics (proportions, means and standard deviations, medians and interquartile ranges) throughout the study. Clinical characteristics of patients in the three cohorts were compared using chi-square tests for dichotomous variables and analyses of variance for continuous variables. We first correlated S_{aO_2} and S_{pO_2} in Cohort 1 using an intra-class coefficient of correlation (ICC) calculated from a two-way mixed effect model, with its 95% confidence interval. We also assessed graphically the agreement between the two measures using a Bland–Altman diagram [15]. In the three cohorts, we then plotted S_{aO_2} against P_{aO_2} to represent oxygen–haemoglobin dissociation curves. We also cross-tabulated the results of S_{aO_2} and P_{aO_2} . In order to demonstrate the effect of arterial pH on the affinity of oxygen for haemoglobin [16], separate dissociation curves were also plotted after separating the cohorts into two groups at the median value of pH and summarised using local polynomial regression (locally estimated scatterplot smoothing [17]). By combining Cohort 1 and 2 (*i.e.*, the two cohorts of patients with COPD), we calculated the false positive and false negative rates of S_{aO_2} at the thresholds of $\leq 88\%$ (*i.e.*, the American prescription threshold) and $\leq 92\%$ (*i.e.*, the British screening threshold) to identify severe hypoxaemia defined according to: 1) the Nocturnal Oxygen Therapy Trial (NOTT [1]) criteria; 2) $P_{aO_2} \leq 55$ mmHg; or 3) $P_{aO_2} < 60$ mmHg regardless of oedema, haematocrit or ECG findings. From the same two cohorts, we constructed receiver operating characteristics (ROC) curves to determine the thresholds of saturation at which severe hypoxaemia is either ruled in or ruled out (*i.e.*, false positive or negative results of 0%). Finally, we used Cohort 3 to validate the results obtained from patients with COPD (Cohorts 1 and 2). All the analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

Patients

Patient characteristics are summarised in table 1. As expected, patients on LTOT (Cohort 2) had more severe hypoxaemia than those with nocturnal oxygen desaturation alone (Cohort 1). Although patients on LTOT were on average mildly hypercapnic, mean pH was normal (median: 7.42; interquartile range: 7.38–7.44), presumably indicating clinical stability when LTOT was initiated. Among the 240 patients who participated in the INOX trial (Cohort 1) and the 212 patients on LTOT (Cohort 2), 33 (14%) and 56 (26%) had a P_{aO_2} in the range of 56 to 59 mmHg, respectively.

Correlation between S_{aO_2} and S_{pO_2}

S_{aO_2} and S_{pO_2} were moderately correlated (ICC: 0.43; 95% CI: 0.32–0.53; n=240, all from Cohort 1; supplementary Figure 1S). The mean±SD difference between the two measures was 0.6±2.0%. The Bland–Altman diagram indicates that the difference did not vary in a systematic pattern over the range of measurements (figure 1).

S_{aO_2} to predict P_{aO_2}

The relation between S_{aO_2} and P_{aO_2} in patients with COPD (Cohort 1 and Cohort 2) and in the validation cohort (Cohort 3) is shown in figure 2. They represent in effect oxygen–haemoglobin dissociation curves.

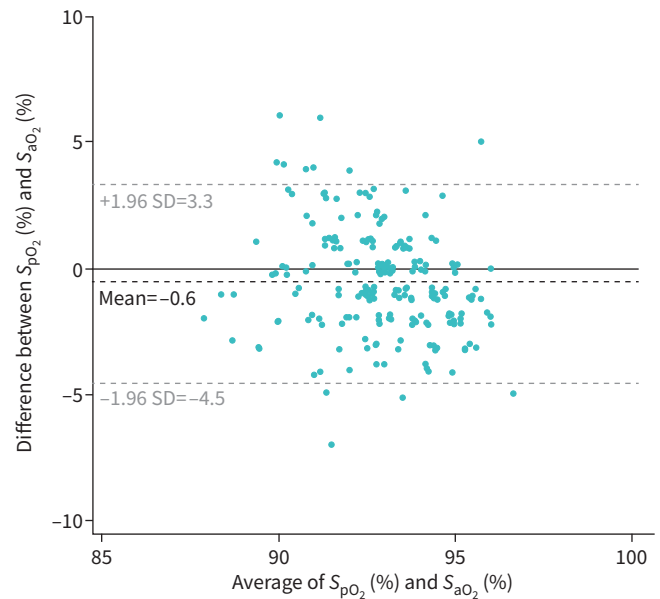


FIGURE 1 Bland-Altman diagram: agreement between pulse oximetry saturation (S_{pO_2}) and arterial oxygen saturation (S_{aO_2}) in the cohort of patients with isolated nocturnal oxygen desaturation ($n=240$).

Cross-tabulation of S_{aO_2} and P_{aO_2} is presented in supplementary Tables 1S and 2S. The dissociation curves and the cross-tabulation of S_{aO_2} and P_{aO_2} indicate the wide variability of P_{aO_2} for a given S_{aO_2} , and conversely, the wide variability of S_{aO_2} for a given P_{aO_2} . The significant effect of pH on the affinity of oxygen for haemoglobin is also demonstrated in supplementary Figure 2S.

Saturation to prescribe LTOT ($\leq 88\%$) or to screen for patient selection ($\leq 92\%$)

Scatter plots of S_{aO_2} values in patients with severe hypoxaemia and those with isolated nocturnal desaturation are presented in figure 3. Among the 240 patients fulfilling the indication for nocturnal oxygen alone, four had a $S_{aO_2} \leq 88\%$ (false positive rate: 1.7%). S_{aO_2} was $>88\%$ in 84 of the 212 patients on LTOT (false negative rate for LTOT prescription: 39.6%) (table 2). Table 2 also includes the false positive and false negative rates of S_{aO_2} at the threshold of $\leq 88\%$ to detect severe hypoxaemia defined as $P_{aO_2} \leq 55$ mmHg or $P_{aO_2} < 60$ mmHg (regardless of oedema, haematocrit and ECG findings). At the S_{aO_2} screening threshold of $\leq 92\%$, 4.7% (10 out of 212) of the truly hypoxaemic patients would not have been referred for further evaluation.

Saturation thresholds to rule in or rule out the indication of LTOT

From the ROC analysis, we determined in Cohorts 1 and 2 that a S_{aO_2} threshold of $\leq 87\%$ rules in the indication of LTOT according to the NOTT criteria (*i.e.*, false positive rate=0%) while a S_{aO_2} threshold of $\geq 96\%$ rules out the indication of LTOT (*i.e.*, false negative rate=0%) (figure 4 and supplementary Table 6S).

Validation study

The false positive and false negative rates in the determination of severe hypoxaemia ($P_{aO_2} \leq 55$ mmHg or $P_{aO_2} < 60$ mmHg) at a S_{aO_2} threshold of $\leq 88\%$ are shown in table 2. We determined, from the ROC analysis, that a $S_{aO_2} \leq 82\%$ rules in severe hypoxaemia defined as $P_{aO_2} \leq 55$ mmHg (*i.e.*, false positive rate=0%), while a $S_{aO_2} \geq 92\%$ rules out severe hypoxaemia (*i.e.*, false negative rate=0%) (supplementary Table 7S). Similarly, a $S_{aO_2} \leq 88\%$ rules in severe hypoxaemia defined as $P_{aO_2} < 60$ mmHg, while a $S_{aO_2} \geq 94\%$ rules out severe hypoxaemia (supplementary Table 8S).

Discussion

Our findings question the validity of using oxygen saturation alone for the prescription of LTOT in COPD. First, as others [8–10], we observed that S_{pO_2} and S_{aO_2} were only moderately correlated. Also, in a recent study [18], the mean \pm sd difference between S_{pO_2} and S_{aO_2} ($S_{aO_2} - S_{pO_2}$) was remarkably similar to what we found (-0.6 ± 2.6 in Ekström's study *versus* -0.6 ± 2.0 in ours). Second, although not measured with pulse oximetry, pH may have, as predicted by physiology, a significant effect on the relation between S_{aO_2} and

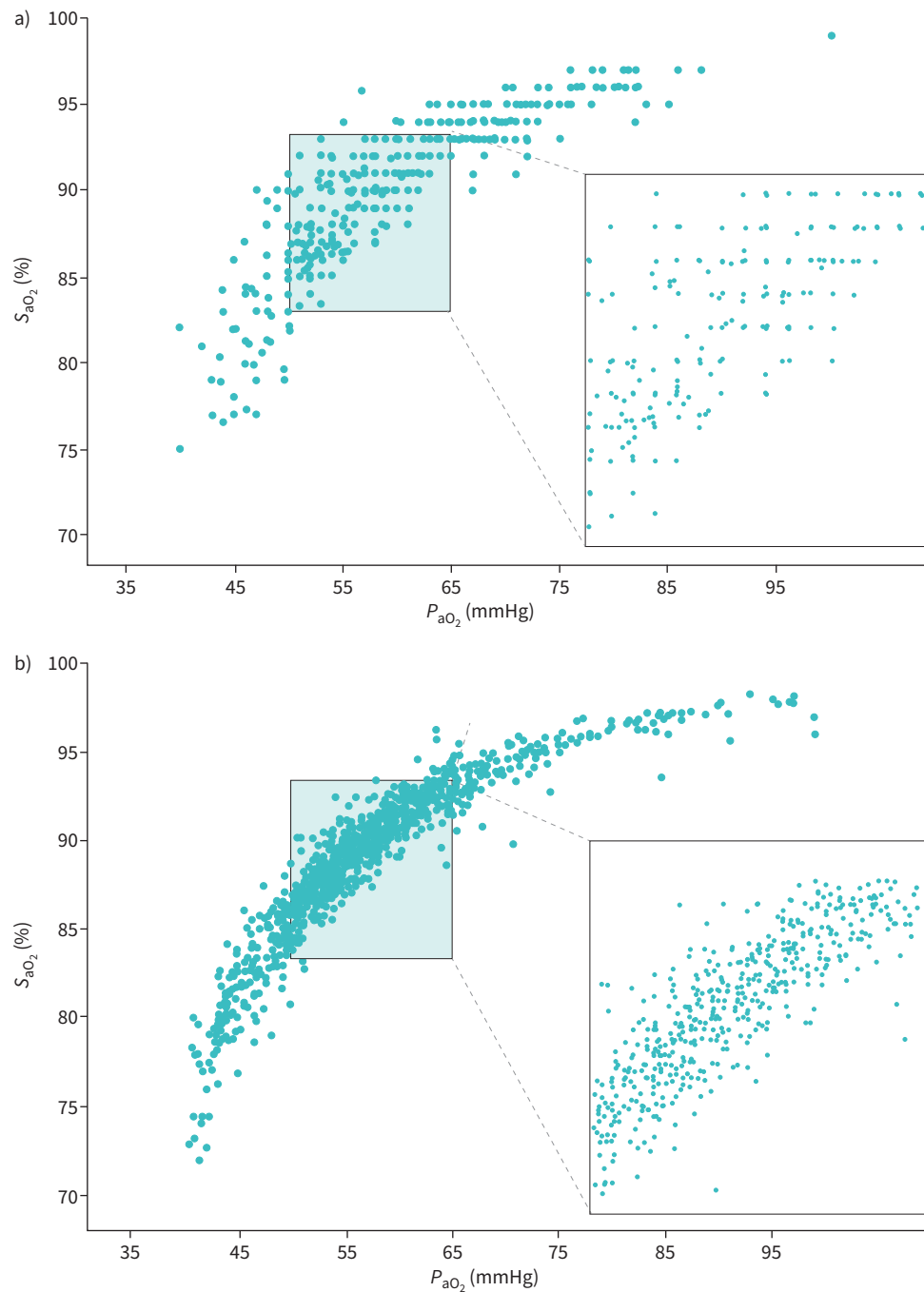


FIGURE 2 The relation between arterial oxygen saturation (S_{aO_2}) and arterial oxygen tension (P_{aO_2}). a) Patients with COPD: $n=452$. b) Validation cohort: $n=848$.

P_{aO_2} as demonstrated by the dissociation curves (figure 1 and supplementary Figure 1S). Third, by using saturation alone, patients are much more often denied LTOT (false negative rate: 40%) than they are prescribed LTOT when it is not indicated (false positive rate: 2%). Fourth, our data suggest that the thresholds of $\leq 82\%$ or $\geq 96\%$ to either rule in or rule out the indication of LTOT may be considered. Even at these thresholds, several factors limit the accuracy of cutaneous pulse oximetry to determine whether LTOT is indicated. These factors include: 1) the precision of the currently available pulse oximeters [19]; 2) the potential for technical errors with their use; 3) the shape of the oxygen–haemoglobin dissociation curve, which may vary due to several unknown or unmeasured variables such as arterial blood pH and temperature [20]; and 4) the imperfect correlation between S_{aO_2} and S_{pO_2} .

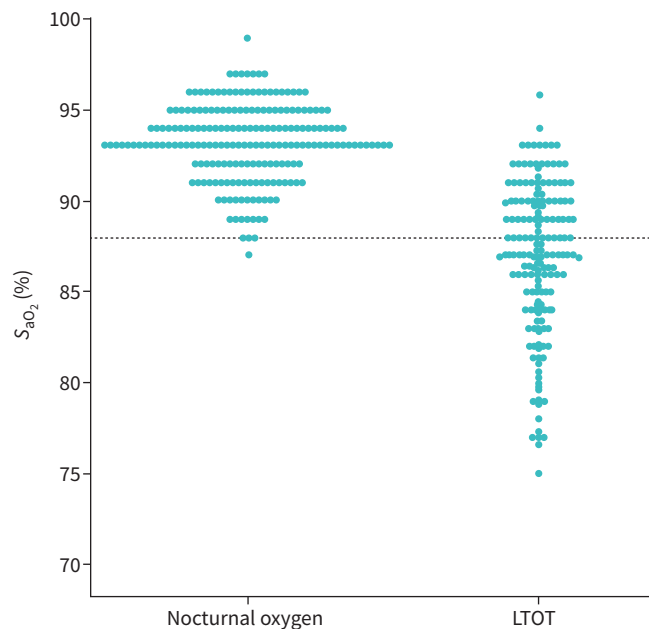


FIGURE 3 Scatter plot of the individual saturation values in patients on long-term oxygen therapy (LTOT) (n=212) and those with isolated nocturnal oxygen desaturation (n=240). The dashed line is located at the saturation threshold of 88%. S_{aO_2} : arterial oxygen saturation.

The reasons why arterial puncture to determine the indication of LTOT has been abandoned in several jurisdictions are unclear since other reports have also underlined the limitations of pulse oximetry [11, 21, 22]. Yet, arterial puncture, most often of the radial artery, is a safe and simple procedure. With the exception of local pain, bruising and haematoma, clinically significant complications are rare [23, 24]. Local pain may be decreased by local anaesthetic infiltration or the application of ice prior to the puncture [25, 26]. Topical anaesthetics do not seem to be effective to reduce pain [27]. The technique can be performed by several health professionals after minimal training [28–30]. Successful punctures may be obtained in almost 90% of cases [8]. The use of ultrasonography to guide arterial puncture of the radial artery does not seem to improve success rate compared with the conventional technique [31]. Blood gas analysers are found in most hospitals. Portable blood gas analysers are also available, with performance similar to that of conventional laboratory blood gas analysers [32]. Cost of arterial puncture is minimal and hardly an issue when the outcome is LTOT, a major cost driver in the management of COPD [33].

ABG measurement has its own limitations. It does not provide continuous data. Measurement errors are also possible. Air bubbles in syringe increases P_{aO_2} , while elevated temperature and delayed analysis has the opposite effect [34, 35]. Transient hyperventilation occurring during arterial puncture may be sufficient to acutely increase P_{aO_2} , a situation that will not reflect the chronic state of hypoxaemia [36]. Acute respiratory

TABLE 2 False positive and false negative rates of arterial oxygen saturation (S_{aO_2}) at the threshold of $\leq 88\%$ to identify severe hypoxaemia in COPD

Severe hypoxaemia defined as	$S_{aO_2} \leq 88\%$ false positive rate		$S_{aO_2} \leq 88\%$ false negative rate	
	COPD (Cohort 1+2)	Validation (Cohort 3)	COPD (Cohort 1+2)	Validation (Cohort 3)
NOTT criteria [1] %	1.7 [#]		39.6 [#]	
$P_{aO_2} \leq 55$ mmHg %	4.7 [¶]	3.3 [†]	21.9 [¶]	15.7 [†]
$P_{aO_2} < 60$ mmHg %	0.5 [¶]	0 [†]	45.4 [¶]	40.3 [†]

NOTT: Nocturnal Oxygen Therapy Trial; P_{aO_2} : arterial oxygen tension. #: details are provided in supplementary Table 3S. ¶: details are provided in supplementary Table 4S. †: details are provided in supplementary Table 5S.

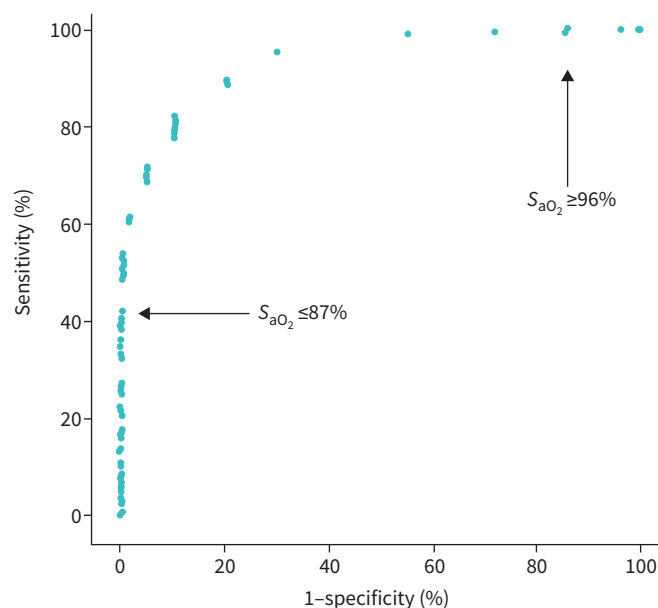


FIGURE 4 Receiver operating characteristics (ROC) curve: sensitivity and specificity of arterial oxygen saturation (S_{aO_2}) at varying thresholds to detect severe hypoxaemia (arterial oxygen tension (P_{aO_2}) ≤ 55 mmHg or P_{aO_2} of 56 to 59 mmHg with evidence of cor pulmonale or erythrocythaemia) at the level to which long-term oxygen therapy (LTOT) is indicated according to the Nocturnal Oxygen Therapy Trial (NOTT) criteria. This analysis combined Cohorts 1 and 2 (*i.e.*, the two cohorts of patients with COPD). The arrows indicate the saturation thresholds at which the false positive rate ($S_{aO_2} \leq 87\%$) and false negative rate ($S_{aO_2} \geq 96\%$) are null.

alkalosis on ABG measurement must alert clinicians to this possibility. The analysis of capillary blood, either arterialed or not, has been proposed as an alternative to ABG measurement. At least two separate meta-analyses comparing capillary and ABG have been published [37, 38]. RICHTER *et al.* [38] developed regression models to predict ABG (including P_{aO_2}) from capillary blood gas values. The authors found excellent predictability of the models and emphasised the potential of capillary blood gases in the management of acute respiratory conditions, without mentioning chronic conditions. ZAVORSKY and colleagues [37] found that earlobe sampling better predicts P_{aO_2} (adjusted $r^2=0.88$, mean bias=3.8 mmHg compared to arterial) than fingertip sampling (adjusted $r^2=0.48$, mean bias=11.5 mmHg compared to arterial). The authors concluded that, in most circumstances, sampling blood from earlobe but not from the fingertip may be, in some circumstances, appropriate as a replacement for P_{aO_2} , unless precision is required.

A limitation of our study is that we determined the false positive and negative rates of saturation to identify severe hypoxaemia as well as the saturation thresholds to rule in or rule out the indication of LTOT on the basis of S_{aO_2} (not S_{pO_2}). Also, ABGs in our cohorts of patients with COPD were obtained from different analysers. In this regard, a study has found that differences in P_{aO_2} values from measurements performed on different blood gas analysers in different laboratories are negligible [39]. Temperature, a significant factor affecting the binding of oxygen to haemoglobin, was not taken into account.

Conclusion

Our study confirmed that S_{aO_2} and S_{pO_2} are only loosely correlated. We found that several patients who qualify for LTOT would be denied treatment using a S_{aO_2} prescription threshold $\leq 88\%$ or a screening threshold $\leq 92\%$. We therefore conclude that oxygen saturation (S_{aO_2} , and *a fortiori* S_{pO_2}) is not an adequate replacement of direct P_{aO_2} measurement for prescribing LTOT or for screening for further assessment of eligibility for LTOT. If chronic hypoxaemia is suspected, patient evaluation should rely on ABG measurement. This practice has its own limitations, since it represents a static and instantaneous measure that may not reflect patients' long-term oxygenation status. However, it has the merit to be aligned with the current indications for LTOT that were defined by the NOTT and the British Medical Research Council trial.

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Conflict of interest: None declared.

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