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ORIGINAL RESEARCH

Time to Steady State after Changes in FIO_2 in Patients with COPD

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Abstract

Background: **International guidelines recommend that when changing FIO_2 in patients with COPD receiving Long-Term Oxygen Therapy (LTOT), 30 minutes should be waited for steady state before measurement of arterial blood gasses. This study evaluates whether 30 minutes is really necessary, as a smaller duration might improve the logistics of care, potentially reducing the time spent by patients at the out-patient clinic.** ***Methods:*** **12 patients with severe to very severe COPD according to the GOLD guidelines were included. Patients had a median FEV_1% of 23% of the predicted value (range 15–64%), median FEV_1/FVC 0.43 (range 0.26–0.63), and chronic respiratory failure necessitating LTOT, 1–4 liters/minute, minimum 16 hours/day. Following a FIO_2 reduction (wash out), arterial blood gases were measured at 0, 1, 2, 4, 8, 12, 17, 22, 32 and 34 minutes. FIO_2 was then increased to baseline levels (wash in) and blood gasses measured at 0, 1, 2, 4, 8, 12, 17, 22, 32, and 34 minutes. Data were analyzed to examine the dynamics of arterial PO_2 and saturation (SO_2) wash out and wash in by calculating the time constants, tau (τ), and to evaluate the time required to reach values which might be considered clinically stable, defined as PO_2 within 0.5 kPa and SO_2 within 1% of equilibrium values.** ***Results:*** **For arterial PO_2 values of time constants were about 3 minutes and similar for both wash out and wash in. A median of 5 minutes was required to reach clinically stable values of PO_2 in both wash out and wash in, with 7–8 minutes sufficient in 75% of patients, and in the worst case 14 minutes. For SO_2, values of the time constant were 4.5 and 1.4 minutes for wash out and wash in, respectively. The time required to reach clinically stable values was different in the two phases. For wash out the median time was 7.4 minutes, and in the worst case 15.6 minutes. For wash in the median time was 2.6 minutes and in worst case 6.8 minutes. No significant changes in PCO_2 or pH were seen during FIO_2 changes.** ***Discussion/Conclusion:*** **This study shows that oxygen equilibration relevant for clinical interpretation requires only 10 minutes following an increase and 16 minutes following a decrease in FIO_2. over the range studied.**

Introduction

Patients suffering from Chronic Obstructive Pulmonary Disease (COPD) can require Long Term Oxygen Therapy (LTOT), the prevalence of which is between 14 and 52 per 100,000 [1]. Adjusting inspired oxygen fraction (FIO_2) for patients in need of LTOT can be time consuming and for this vulnerable group of patients a very distressing process, both at the hospital and out-patient clinic. Current guidelines [2] recommend that 20–30 minutes be waited following change in FIO_2 before a blood sample be drawn to evaluate the effect. However, this recommendation refers to a review of the literature by Woolf in the 1970s [3] and has not been questioned since.

Keywords: COPD, LTOT, oxygen equilibrium

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Woolf's review concluded on a number of studies from that period involving changes in FIO_2 and monitoring of the dynamic response in arterial blood in patients with COPD. In these studies the variable chosen to describe the response to oxygen changes is not consistent, with either PO_2 [4, 5], or SO_2 [6] used to evaluate steady state. Studies have not investigated both decrease (oxygen wash out) and increase (oxygen wash in) with those in spontaneously breathing patients considering only wash out [4, 5, 7, 8] and a single study in mechanically ventilated patients considering only wash in [7]. Studies have also used different sampling times, with only one [5] measuring frequently enough in the early phase to characterize the fast dynamics. In addition, the end point for the oxygen change is analyzed in different ways, with some looking at return to baseline [4, 5], others at the time to reach 90% of the final value (T90) [6, 7].

The former does not relate to clinical practice where, for example, reaching within 1% of the final oxygen saturation is adequate for clinical interpretation. The latter suffers from the fact that it is dependent on size of the oxygen step. The time constant tau (τ), was only calculated in one study, in patients with cardiac disease [8]. Finally, none of the studies were performed within ranges of FIO_2 relevant for daily clinical practice, with typically FIO_2 changed from room air to 100%, a range only relevant when using high values of FIO_2 measuring shunt in patients.

This study revisits the question of the necessary time to reach oxygen equilibration after change in FIO_2. In doing so, both arterial PO_2 and saturation (SO_2) are considered, as are both the wash in and wash out of oxygen. Sampling times are identified sufficiently close to equilibrium so as to provide clinical interpretation, and the step changes in FIO_2 used are consistent with changes seen when adjusting LTOT.

Methods

Patients

Twelve patients, 3 males and 9 females median age 61.5 years (range 55.75–67.25), were included. Patients had severe to very severe COPD according to GOLD-guidelines [9] with median FEV_1% of 23 (% predicted, range 15–64%) and a median FEV_1/FVC of 0.43 (range 0.26-0.63). All patients had chronic respiratory failure receiving oxygen therapy (1–4 liters/minute, 16–24 hours per day) as part of routine clinical care, all were they evaluated, in steady state, within 3 months prior to the study. None of the patients had had exacerbations within 2 months prior to the study. All patients had a Medical Research Council-score (MRC-score) [10] of 4 and a median PCO_2 value on inclusion of 42 mmHg (range 40-57). Two patients were current smokers. The remaining were all former smokers with a median of 37.5 (range 25-45) pack-years.

Oxygen therapy was given as prescribed in the hours prior to the examination. After arriving to the experimental setting, the patients rested for 30 minutes before the study period. Patients had a radial arterial cannula placed by an experienced anesthesiologist. Pulse oximetry was used to continuously monitor O_2 saturation for safety purposes. Arterial blood was sampled twice at baseline and FIO_2 was reduced. In 10 patients inspired oxygen was reduced by removing the nasal catheter, and in two patients inspired oxygen was reduced from 3 to 1 l/min and 4 to 2 l/min, respectively, as severe desaturation had previously occurred in these patients during routine clinical management. Arterial blood samples were drawn at the time 0, 1, 2, 4, 8, 12, 17, 22, 32 and 34 minutes, following FIO_2 reduction (wash out).

If pulse oximeter saturation fell below 85% during the study period patients were immediately excluded, oxygen supply re-instituted and the patients were observed until saturation returned to baseline.

Nasal canulas were then re-inserted or oxygen increased to baseline levels (wash in), and the same arterial sampling regime used. For safety reasons, i.e. to ensure that the patient retuned to baseline levels, the arterial canulas were left in place for 30 minutes following completion of the study and a final blood sample taken. Each blood sample was analysed to obtain acid-base and blood gas status (ABL 835 and 837-Radiometer, Copenhagen, Denmark) by measuring PO_2, PCO_2 and pH.

Ethics

The study was approved by the local Ethical Committee. All patients were informed verbally and in writing at least two days prior to the examination and written consents were obtained prior to inclusion. Patients were excluded if they were unable to understand verbal and written information.

Data analysis

Values of pH, PCO_2, PO_2 and SO_2 from the arterial blood gasses are reported for the start and end of both wash in and wash out periods to illustrate the degree to which oxygenation was changed on an individual patient basis and to ensure that no dramatic changes occurred in respiratory drive when changing FIO_2, as would be apparent by changes in pH and PCO_2.

Data were analyzed to examine the dynamics of PO_2 and SO_2 wash out and wash in, and to evaluate the time required to reach values which might be considered clinically stable. Data describing the dynamics is plotted for each patient and a single exponential curve fitted to the wash in and wash out phases of each variable, with time constant tau (τ), calculated for each case as suggested previously [8]. To investigate whether those with greater obstructive impairment had slower equilibrium, basal PO_2 levels, values of FEV_1% and values of FEV_1/FVC were correlated with values of time constants. To evaluate the time taken to achieve clinical stability we defined two parameters: Tp, the time taken for PO_2 to be within 4mm Hg of steady state value; and Ts, the time taken for SO_2 to be within 1% of the steady-state value, with these values chosen based upon local clinical opinion as relevant to actual clinical practice. Steady state values were read from

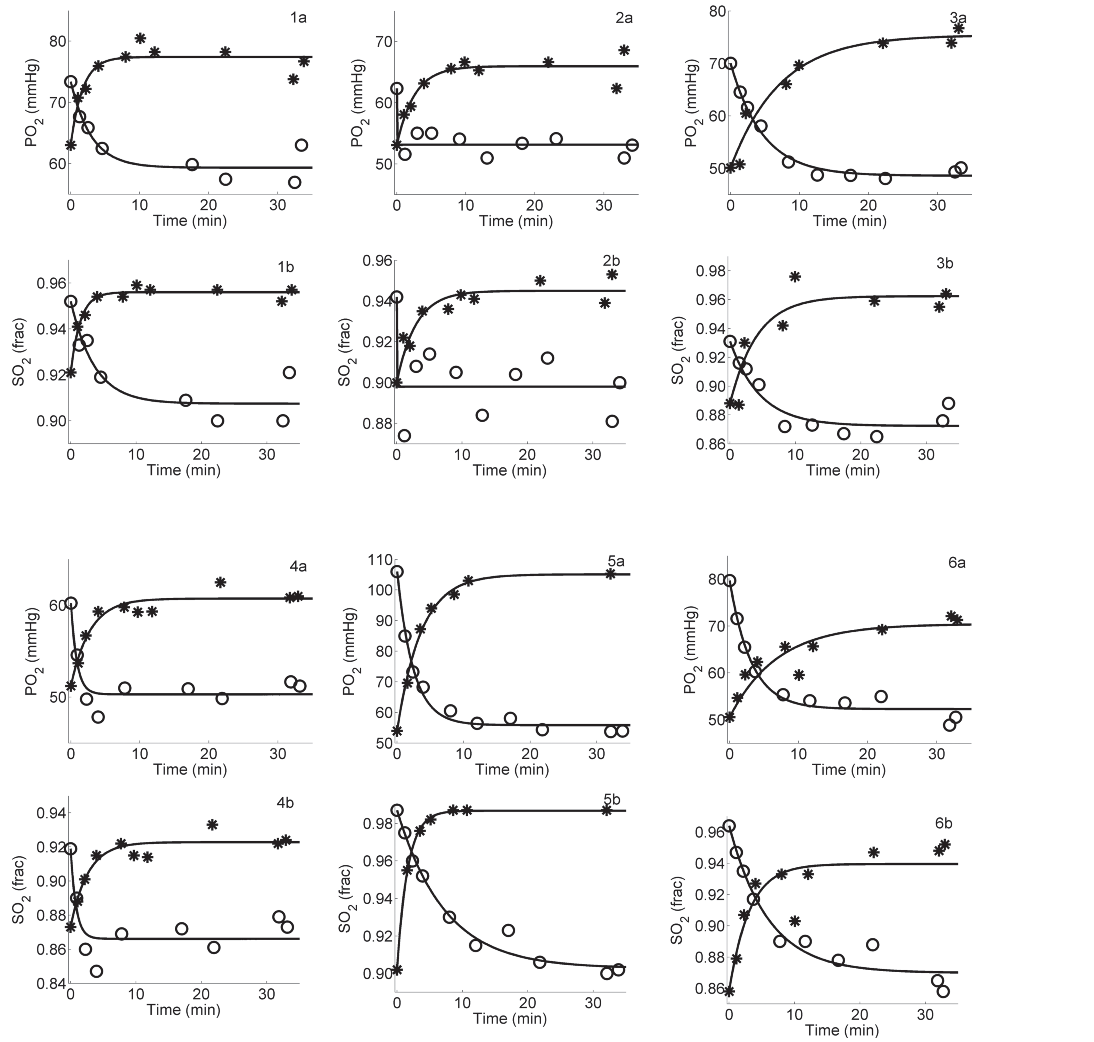

Figure 1. Measured values, from arterial blood gases, from patients 1 to 6, for wash out (circles) and wash in (stars) of PO_2 (1a to 6a) and SO_2 (1b to 6b), plus single exponential curves fitted to measured values.

the plateau of the exponential curve. Values for Tp and Ts were calculated for both wash out and wash in.

Results

Figures 1 and 2 illustrate the dynamics of oxygen change following wash out and wash in in all 12 patients. Values of pH, PCO_2, PO_2 and SO_2 at the beginning and end of these phases are given in Table 1a and b and values of lung function tests (FEV_1 %, FEV_1/FVC), time constants (τ) and time to reach clinical stability (Tp, Ts) are given in Table 2.

In 2 patients (8 and 10) coagulation of blood in a batch of faulty heparinized syringes meant that wash in curves could not be drawn. A further 7 samples were not taken (patient 5 wash in, 3 samples; patient 12 wash in, 3 samples, wash out 1 sample). Of the remaining 213 blood samples, 10 were excluded, 7 due to visible air bubbles in samples (patient 1 wash out, 2 samples; patient 7 wash out, 1 sample; patient 9 wash in, 2 samples; patient 10 wash out, 2 samples) and a further 3 due to clearly incorrect measurement values as indicated by an arterial PCO_2 more than 6 mm Hg outside the range of all other values (patient 3 wash in, 2 samples; patient 4 wash out, 1 sample).

Values of lung function, PCO_2 and oxygenation are typical of those seen in patients with COPD in need of LTOT (Table 1a and b, Table 2). Changes in PO_2 and SO_2 during the experiment were typical of those seen in clinical practice with PO_2 varying from 49 mm Hg to 108 mmHg kPa, and SO_2 from 86 to 99 % (Table 2). At the end of the study patient values for SO_2 and PO_2 were not significantly different from the values measured at the beginning of the study period (p = 0.23 for PO_2 and p = 0.33 for SO_2). In addition there was no significant change in PCO_2 and pH during changes in oxygenation (p = 0.23 for PCO_2 and p = 0.32 for pH), indicating that compensatory changes in respiration were unlikely, as a change in respiration would be expected to have caused alterations in PCO_2 due to CO_2 diffusion ability.

Figures 1 and 2 illustrate a wide range of response times to reach steady state, but with little change occurring in either of the variables 10 minutes after FIO_2 change. Table 2 quantifies these changes. For PO_2 the median value of τ were 2.9 minutes during wash out and 2.4 minutes during wash in, with no significant differences between these (p = 0.24). Similar values were also seen for Tp in the two phases with a median time of 5.4 and 2.6 minutes, with

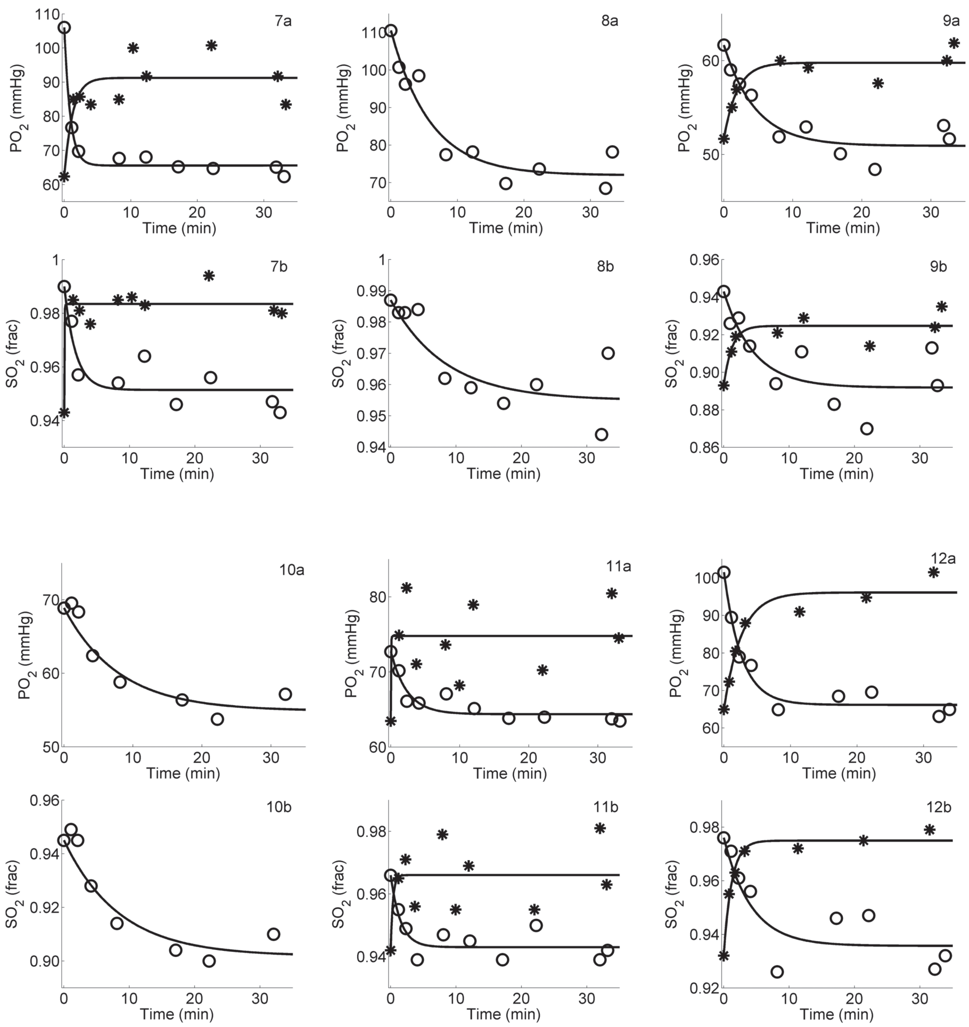

Figure 2. Measured values from arterial blood gases from patients 7 to 12, for wash out (circles) and wash in (stars) of PO_2 (7a to 12a) and SO_2 (7b to 12b), plus single exponential curves fitted to measured values.

no significant differences between these (p = 0.17). The maximum value of Tp was 13.8 minutes (patient 8). For SO_2, median values of τ were 4.5 minutes and 1.4 minutes for wash out and wash in respectively. Values for Ts were also different in the two phases, with a median time to reach 1 % of equilibrium value of 6.7 minutes for wash out and 1.9 minutes for wash in. The maximum values of Ts were 15.6 minutes (patient 5) and 8.3 (patient 3) minutes in these phases. In 3 patients (2, 4, and 9) there appeared to be cyclic variation in SO_2 of greater than 2% during wash out. Little correlation was seen between values of time constants with patients' condition as described by basal PO_2 levels, FEV_1% or FEV_1/FVC, with calculated values of correlation coefficients (r_2) never exceeding 0.2.

Discussion

When changing inspired oxygen level in patients with COPD, current guidelines recommend waiting a period of 20–30 minutes before measuring the arterial blood gasses. In American centers common practice is to wait 10–20 minutes. This study shows that an oxygen equilibration relevant for clinical interpretation is available only 10 minutes following an increase and 16 minutes following a decrease in FIO_2, which may change practice in European centers and validates American practice.

Unlike previous studies [3], this study has investigated oxygen equilibration, systematically looking at wash out and wash in, PO_2 and SO_2 dynamics, selecting appropriate sample times, using FIO_2 changes typical of clinical practice and defining endpoints that have clinical relevance. Previous studies have investigated oxygen dynamics only for wash out in spontaneously breathing patients [4–6], using either PO_2 [4, 5] or SO_2 [6] as measured variables. This study has shown the need for investigating the dynamics of both PO_2 and SO_2 and understanding the relationship between them when interpreting results. Sampling times were selected to enable description of the fast kinetics of change in oxygenation, with previously only the study by Sherter et al. [5] having frequent sampling. Sherter, however, investigated only wash out, used an FIO_2 step from 1.0–0.21 and an endpoint of return to baseline.

This large step in FIO_2 is relevant if measuring shunt in the patients but inconsistent with clinical practice and return to baseline an unnecessary endpoint for clinical

Table 1a. Oxygen administered, acid-base and oxygenation status in the 12 patients at the start and the end of oxygen wash out

	Wash out								
	Start					End			
	O_2, l/min	pH	PCO_2 (kPa)	SO_2 (%)	PO_2 (kPa)	pH	PCO_2 (kPa)	SO_2 (%)	PO_2 (kPa)
1	0	7.46	5.7	95	9.8	7.44	5.8	90	7.6
2	0	7.46	5.0	93	7.9	7.47	5.0	88	6.8
3	1	7.40	9.0	93	9.4	7.42	8.6	88	6.6
4	1	7.36	8.3	91	7.9	7.38	7.9	86	6.9
5	0	7.43	5.5	98	12.5	7.45	5.4	90	7.2
6	0	7.43	7.5	96	10.4	7.44	7.4	87	6.5
7	0	7.44	5.3	98	10.5	7.45	5.3	95	8.7
8	0	7.42	5.4	98	14.4	7.43	5.5	94	9.8
9	0	7.36	8.7	94	8.1	7.39	8.1	90	7.1
10	0	7.40	6.5	94	8.1	7.41	6.3	91	7.6
11	2	7.46	4.9	95	9.2	7.46	4.8	94	8.5
12	0	7.46	5.3	97	12.8	7.46	5.1	93	8.6

Table 1b. Oxygen administered, acid-base and oxygenation status in the 12 patients at the start and the end of oxygen wash in and 30 minutes following the end of wash in.

	Wash in												
	Start					End				30 min			
	O_2, l/min	pH	PCO_2 (kPa)	SO_2 (%)	PO_2 (kPa)	pH	PCO_2 (kPa)	SO_2 (%)	PO_2 (kPa)	pH	PCO_2 (kPa)	SO_2 (%)	PO_2 (kPa)
1	1.0	7.44	6.1	92	8.4	7.45	5.9	96	10.2	7.44	5.7	94	8.7
2	1.5	7.47	4.7	90	7.1	7.44	5.1	95	9.1	7.46	4.8	93	7.9
3	3.0	7.43	8.3	89	6.7	7.40	8.8	96	10.2	7.40	9.0	96	9.7
4	3.0	7.38	7.9	87	6.8	7.38	7.8	92	8.1	7.38	7.8	92	8.1
5	2.0	7.45	5.4	90	7.2	7.43	5.6	99	14.2	7.43	5.8	98	14.0
6	1.5	7.43	7.4	86	6.7	7.41	7.7	95	11.2	7.43	7.3	95	9.1
7	1.0	7.45	5.3	94	8.3	7.42	5.6	98	11.1	7.42	5.4	97	10.1
8	1.0	*	*	*	*	*	*	*	*	7.41	5.7	98	10.6
9	2.0	7.38	8.5	89	6.9	7.36	8.8	93	8.2	7.37	8.4	93	8.4
10	1.5	*	*	*	*	*	*	*	*	7.40	6.4	93	8.8
11	4.0	7.46	4.9	94	8.4	7.46	5.2	96	9.9	7.45	5.1	95	9.7
12	2.0	7.45	5.2	93	8.6	7.45	5.3	97	12.9	7.47	5.0	95	9.3

*Data missing, see text for details.

evaluation of a patient. In contrast, we have defined reaching a value of PO_2 4 mm Hg from baseline or a value of SO_2 1% from baseline as clinically relevant endpoints sufficient for interpretation of the patient. This definition is different to previous studies where the time to baseline is represented either as return to baseline or 90% (T90) of the change in SO_2 or PO_2. Return to baseline has been criticized by other authors, and other studies [6, 7] have used time to reach 90% of the equilibrium (T90) as an endpoint. However, defining an endpoint as 90% of the change means that equilibrium times are dependent on the magnitude of the FIO_2 change, and indeed studies using this endpoint have used an FIO_2 step of 1.0–0.21, which does not reflect clinical practice.

This study evaluates the dynamics of both PO_2 and SO_2, and in that context it important to realize the theoretical difference expected in the dynamics of these variables on changing FIO_2. These differences can be understood by looking at the oxygen dissociation curve (ODC), Figure 3. During wash out both PO_2 and SO_2 will fall. For a patient with a SO_2 = 97% and a PO_2 = 90 mm Hg (A – Figure 3), reducing oxygen will result in a rapid fall in PO_2 with little initial change in SO_2, due to the flat shape of the ODC around these values. In contrast the pattern changes when one passes the shoulder of the ODC. For a patient with SO_2 = 84 % and PO_2 = 50 mm Hg (B - Figure 3), increasing oxygen will result in a rapid increase in both SO_2 and PO_2 due to the linear shape of the ODC around these values.

Table 2. Lung function, time constants (τ) and time to clinical steady state (Tp, Ts) for oxygen wash out and wash in, in each of the 12 patients

			Wash out				Wash in			
	Lung function		PO_2		SO_2		PO_2		SO_2	
	FEV_1%	FEV_1/FVC	τ (min)	Tp (min)	τ (min)	Ts (min)	τ (min)	Tp (min)	τ (min)	Ts (min)
1	33	0.45	3.0	4.0	3.6	5.4	1.7	2.4	1.5	1.9
2	44	0.52	0.03	0.1	0.03	0.1	2.6	3.2	3.0	4.5
3	17	0.27	4.7	8.1	4.6	8.1	7.2	13.7	4.1	8.3
4	15	0.41	0.9	0.9	0.8	1.4	2.8	2.6	2.6	4.3
5	23	0.40	2.4	6.3	7.3	15.6	3.6	9.5	1.6	3.5
6	16	0.27	3.1	6.3	6.0	13.4	5.0	8.4	3.1	6.8
7	63	0.64	0.9	2.2	1.7	2.4	1.2	2.6	0.03	0.1
8	18	0.38	5.9	13.8	8.4	9.8	*	*	*	*
9	23	0.44	4.6	4.9	4.6	7.5	1.9	1.5	1.3	1.5
10	45	0.48	7.9	10.5	8.5	12.4	*	*	*	*
11	29	0.45	2.4	1.9	1.5	1.3	0.03	0.1	0.3	0.3
12	21	0.30	2.6	5.9	4.2	5.9	2.6	5.6	1.2	1.8

*Data missing, see text for details.

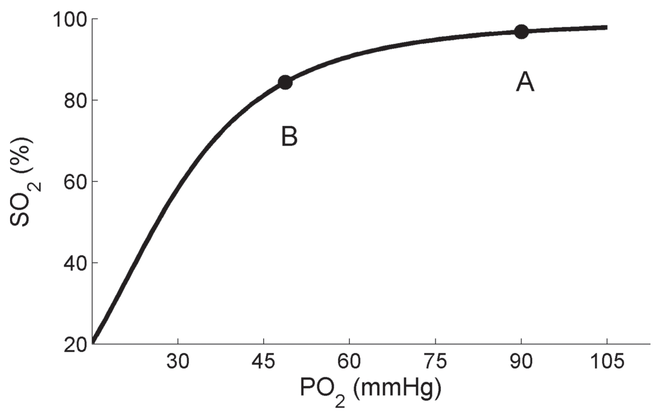

Figure 3. The oxygen dissociation curve (ODC). A and B are used in the text to describe changes in oxygenation from these points.

There are different initial dynamics for SO_2 during wash out and wash in, and care should be taken to interpret results in this context. The Time Constant is, however, different in the individual patients, due to the heterogeneity of the patophysiology of the lungs in this disease entity. This study has been designed to investigate oxygen dynamics in FIO_2 changes typical of those administered to patients suffering from COPD. As such changes in respiratory drive due to over-oxygenation were not expected. This is consistent with very little change in median values of PCO_2 and no change in pH throughout the study period, even though there was some indication of cyclic oxygenation patterns in 3 patients during the wash out phase. Ventilatory volumes could have confirmed changes in respiration; however measurement of these would have required patients to breathe through masks, which may further have increased the risk of changes in respiratory patterns.

This study shows that on adjusting FIO_2 in COPD patients—even those with very severe disease—it is unnecessary to wait 30 minutes before arterial blood sampling, with a maximum of 16 minutes required, and even less on increasing FIO_2.

Declaration of Interest Statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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