

# Capillary PO<sub>2</sub> does not adequately reflect arterial PO<sub>2</sub> in hypoxemic COPD patients

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**Purpose:** To compare arterial (P<sub>a</sub>O<sub>2</sub>) with capillary (P<sub>c</sub>O<sub>2</sub>) partial pressure of oxygen in hypoxemic COPD patients because capillary blood gas analysis (CBG) is increasingly being used as an alternative to arterial blood gas analysis (ABG) in a non-intensive care unit setting, although the agreement between P<sub>c</sub>O<sub>2</sub> and P<sub>a</sub>O<sub>2</sub> has not been evaluated in hypoxemic COPD patients.

**Patients and methods:** Bland–Altman comparison of P<sub>a</sub>O<sub>2</sub> and P<sub>c</sub>O<sub>2</sub> served as the primary outcome parameter if P<sub>c</sub>O<sub>2</sub> values were ≤60 mmHg and the secondary outcome parameter if P<sub>c</sub>O<sub>2</sub> values were ≤55 mmHg. Pain associated with the measurements was assessed using a 100-mm visual analog scale.

**Results:** One hundred and two P<sub>a</sub>O<sub>2</sub>/P<sub>c</sub>O<sub>2</sub> measurement pairs were obtained. For P<sub>c</sub>O<sub>2</sub> values ≤60 mmHg, the mean difference between P<sub>a</sub>O<sub>2</sub> and P<sub>c</sub>O<sub>2</sub> was 5.99±6.05 mmHg (limits of agreement: –5.88 to 17.85 mmHg). For P<sub>c</sub>O<sub>2</sub> values ≤55 mmHg (n=73), the mean difference was 5.33±5.52 mmHg (limits of agreement: –5.48 to 16.15 mmHg). If P<sub>a</sub>O<sub>2</sub> ≤55 (≤60) mmHg was set as the cut-off value, in 20.6% (30.4%) of all patients, long-term oxygen therapy have been unnecessarily prescribed if only P<sub>c</sub>O<sub>2</sub> would have been assessed. ABG was rated as more painful compared with CBG.

**Conclusions:** P<sub>c</sub>O<sub>2</sub> does not adequately reflect P<sub>a</sub>O<sub>2</sub> in hypoxemic COPD patients, which can lead to a relevant number of unnecessary long-term oxygen therapy prescriptions.

**Keywords:** blood gas analysis, COPD, respiratory insufficiency, hypoxemia

## Plain language summary

Patients with COPD can develop severe hypoxemia in the natural course of their disease. If the partial pressure of oxygen (PO<sub>2</sub>) is very low, long-term oxygen therapy (LTOT) is indicated in these patients. To assess PO<sub>2</sub>, arterial blood gas analysis (ABG) serves as the standard method (= gold-standard). Capillary blood gas analysis (CBG; earlobe sampling) is increasingly being used as an alternative, although the accuracy for hypoxemic patients with COPD has not been evaluated. The current trial, therefore, compared ABG with CBG in 102 severely hypoxemic COPD patients. It was shown that CBG does not adequately reflect PO<sub>2</sub> from ABG in hypoxemic COPD patients, which can lead to a relevant number of unnecessary LTOT prescriptions. However, ABG was rated as more painful compared with CBG, although overall pain sensation was moderate.

## Introduction

Blood gas analysis is an essential tool for monitoring respiratory status. The gold-standard method is arterial blood gas analysis (ABG) of blood from the patient's radial artery, an approach that is especially useful for evaluating the partial pressure of oxygen (PO<sub>2</sub>).<sup>1,2</sup> Arterialized capillary blood gas analysis (CBG) serves as a substitute for arterial sampling, which shows several important advantages – CBG is less invasive,<sup>3</sup> can be performed by non-medical staff,<sup>4</sup> requires smaller blood samples,<sup>2</sup>

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and is more economical than ABG.<sup>2</sup> However, it is less useful in the acute setting because an adequate vasodilatation needs to be ensured, which typically lasts for at least 10 minutes.<sup>1,2,5-7</sup>

Different trials have evaluated the agreement between ABG and CBG in terms of PO<sub>2</sub> measurements, with conflicting results; whereas one trial reported close agreement between ABG- versus CBG-derived values over a wide range of PO<sub>2</sub> values,<sup>7</sup> other trials showed wide limits of agreement (LOA).<sup>8,9</sup> A 2007 meta-analysis comparing ABGs to CBGs emphasized that capillary PO<sub>2</sub> (P<sub>c</sub>O<sub>2</sub>) (earlobe sampling) may be an appropriate replacement for arterial PO<sub>2</sub> (P<sub>a</sub>O<sub>2</sub>);<sup>2</sup> however, the authors also pointed out that CBG might not be appropriate if precision is required, based on the fact that the residual standard error (SE) in the regression equation was 6 mmHg.<sup>2</sup> This is of great importance, since, for example, long-term oxygen therapy (LTOT) is based on absolute values of PO<sub>2</sub>. Specifically, LTOT is indicated in patients with PO<sub>2</sub> ≤55 or ≤60 mmHg in the presence of peripheral edema or polycythemia, or with evidence of pulmonary hypertension.<sup>10,11</sup> Importantly, LTOT guidelines differ considerably: while the British Thoracic Society (BTS) guideline recommends ABG in preference to CBG,<sup>10</sup> the German guideline suggests that CBG is appropriate in the non-intensive care unit setting.<sup>12</sup> Of note, Zavorsky et al found that CBG reflects ABG more accurately for lower PO<sub>2</sub>-levels.<sup>2</sup> However, no subgroup analysis was performed for PO<sub>2</sub> values <60 or 55 mmHg, respectively, which are the crucial cut-off points for LTOT indication. For this reason, the present study compared P<sub>c</sub>O<sub>2</sub> and P<sub>a</sub>O<sub>2</sub> in these hypoxemic ranges.

## Patients and methods

The study protocol was approved by the Ethics Committee at Witten/Herdecke University, Witten, Germany, and was undertaken at the Department of Pneumology, Lung Clinic, Cologne Merheim Hospital, Witten/Herdecke University, Germany. The study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. The study was registered at the German Clinical Trials Register (DRKS00010624). Informed written consent was obtained from all subjects. A recruitment period of 6 months was planned and resources calculated accordingly.

## Patients

Patients ≥18 years of age with an established diagnosis of COPD GOLD ≥2 (forced expiratory volume in 1 s [FEV<sub>1</sub>] <80%, FEV<sub>1</sub>/inspiratory vital capacity [IVC] <70%)<sup>13</sup> and P<sub>c</sub>O<sub>2</sub> ≤60 mmHg were included in the study. P<sub>c</sub>O<sub>2</sub> was used as the inclusion criteria because it is the standard

method in Germany for performing blood gas analysis in chronic care.<sup>12</sup>

Exclusion criteria were as follows:

- Cardiorespiratory instability (SpO<sub>2</sub> <80%, despite supplemental oxygen therapy and any of the following: Borg dyspnea scale ≥5, heart rate >140/min, breathing frequency >25/min).
- Absolute contraindication for ABG and relative contraindication for ABG without indication for ABG beyond the present trial as defined previously.<sup>14,15</sup>

## Study design and measurements

The primary aim of the study was to compare P<sub>c</sub>O<sub>2</sub> versus P<sub>a</sub>O<sub>2</sub> in patients with P<sub>c</sub>O<sub>2</sub> ≤60 mmHg. The secondary aims were to compare 1) P<sub>c</sub>O<sub>2</sub> with P<sub>a</sub>O<sub>2</sub> measurements in patients with P<sub>c</sub>O<sub>2</sub> ≤55 mmHg and to assess, 2) arterial (S<sub>a</sub>O<sub>2</sub>), capillary (S<sub>c</sub>O<sub>2</sub>), and peripheral oxygen saturation (S<sub>p</sub>O<sub>2</sub>), 3) arterial (HCO<sub>3</sub><sup>-</sup>) and capillary (HCO<sub>3</sub><sup>-</sup>) standard bicarbonate, 4) partial pressure of arterial to capillary carbon dioxide (P<sub>a</sub>CO<sub>2</sub>/P<sub>c</sub>CO<sub>2</sub>), as well as 5) arterial and capillary pH (pH/pH). A further aim was to compare pain ratings from patients undergoing ABG and CBG, respectively.

Demographic data (age, height, weight, gender, and smoking status) and lung function parameters (full body plethysmography and diffusion tests) were collected from each patient, when available. Patients were seated during the blood gas analyses. If the patient was already on LTOT, supplemental oxygen therapy was stopped for at least 30 minutes, if tolerated by the patient. S<sub>p</sub>O<sub>2</sub> was measured from the right index finger (Oximeter Wrist OX<sub>2</sub>,<sup>®</sup> model 3150, Nonin Medical Inc., Plymouth, MN, USA). If SpO<sub>2</sub> dropped to <80% and the patient became severely dyspneic, supplemental oxygen was administered in order to achieve stable respiratory status (defined as SpO<sub>2</sub> >80%, Borg dyspnea scale <5, heart rate <140/min, and breathing frequency <25/min). In this case, further measurements were performed at the given oxygen flow rate after a stable respiratory status was achieved for at least 30 minutes. A vasodilatory substance (Finalgon<sup>®</sup> Wärmecreme stark, Boehringer Ingelheim, Ingelheim am Rhein, Germany), was applied to one earlobe for 10 minutes before further measurements.<sup>7-9</sup> ABG and CBG (earlobe) were then performed simultaneously by two investigators and processed within 2 minutes (ABL 800 flex, Radiometer Medical ApS, Brønshøj, Denmark). Squeezing and milking of the earlobe, as well as air bubbles in the probe, were strictly avoided. SpO<sub>2</sub> readings were assessed at the time of puncture. ABG was performed on the radial artery according to current recommendations with a thin cannula (BD Eclipse<sup>™</sup> Needle, BD Medical, Franklin Lakes, NJ, USA, 27 G).<sup>14,15</sup>

The intensity of pain experienced during ABG and CBG was then rated by each patient using a 100-mm visual analog scale (VAS; 0= no pain, 50= acceptable pain, 100= maximal pain).<sup>9,16</sup>

## Analysis

The primary aim of the study was to compare P<sub>c</sub>O<sub>2</sub> and P<sub>a</sub>O<sub>2</sub>. This was performed by calculating the 95% lower limit of agreement (LLA) and upper limit of agreement (ULA) for differences between methods, in accordance with the Bland and Altman method.<sup>17</sup> The methods for PO<sub>2</sub> measurement were considered to be in agreement when both limits were in the range of -8 to 8 mmHg.

The statistical test of agreement was then performed by calculating 95% CI for the LLA and ULA. Agreement between the two methods was established when the lower CI limit of the LLA was above -8 mmHg and the upper CI limit of the ULA was below 8 mmHg.

For sample size calculation, an SD of 3.5 mmHg was assumed (based on previous findings by Zavorsky et al<sup>2</sup>) for the subgroup of patients with P<sub>a</sub>O<sub>2</sub> < 70 mmHg (n=227, mean difference =0.7, SD =3.4). Using the assumption of perfect agreement between methods, this resulted in expected LLA and ULA values of -6.86 and 6.86 mmHg, respectively. On the basis of this, the inclusion of 220 subjects was necessary to show agreement between methods at a one-sided alpha level of 0.025 and a power of 80%. LLA and 95% CI were also calculated for the comparison of secondary endpoints. Pain ratings recorded on the 100-mm VAS were compared between methods by paired *t*-tests.

## Results

The study was conducted from June to December 2016. Due to slow recruitment, an analysis of the first 102 patients was performed, which showed that the planned proof of agreement with limits between -8 and 8 mmHg was not possible, even with a larger sample size. As outlined above, planning of the study was based on the assumption of perfect agreement between P<sub>c</sub>O<sub>2</sub> and P<sub>a</sub>O<sub>2</sub> measurements (SD=3.5) leading to expected LLAs of ±6.86 mmHg, so that LLAs can be shown to be ±8 mmHg from zero with 220 patients. In the first 102 patients of our study, the observed SD was 6.05 leading to expected LLAs of ±11.86 mmHg even under the assumption of perfect agreement. Thus, with this larger SD, the desired proof of agreement within ±8 mmHg from zero would not be possible even with an infinite sample size, as the expected LLAs refer to values of individual patients which are not influenced by the number of patients under study. Therefore, the study was stopped prematurely.

The median P<sub>a</sub>O<sub>2</sub> was 56.3 mmHg (interquartile range [IQR]: 50.7–61.4 mmHg), and the median P<sub>c</sub>O<sub>2</sub> was 50.3 mmHg (IQR: 46.0–56.0 mmHg). Seventeen patients (16.5%) were on oxygen during the measurements (n=4: 2 L/min, n=8: 1 L/min, and n=5: 0.5 L/min). Further demographic data, ABG data, and lung function parameters are shown in Table 1.

## Comparison of P<sub>a</sub>O<sub>2</sub> and P<sub>c</sub>O<sub>2</sub> for P<sub>c</sub>O<sub>2</sub> values ≤60 mmHg (primary outcome)

The mean difference between gold-standard P<sub>a</sub>O<sub>2</sub> and P<sub>c</sub>O<sub>2</sub> was 5.99±6.05 mmHg, with an LLA of -5.88 mmHg (95% CI -7.92 to -3.84 mmHg) and an ULA of 17.85 mmHg (95% CI 15.81–19.89 mmHg), Table 2; Figure 1. In 31 of 102 measurements (30.4%), P<sub>a</sub>O<sub>2</sub> was >60.0 mmHg, although P<sub>c</sub>O<sub>2</sub> was ≤60.0 mmHg.

P<sub>c</sub>O<sub>2</sub> overestimated P<sub>a</sub>O<sub>2</sub> in 5 of 102 measurements (4.9%). The mean overestimation in these 5 measurements was 2.98 mmHg (SD ±1.92 mmHg). Conversely, P<sub>c</sub>O<sub>2</sub> underestimated P<sub>a</sub>O<sub>2</sub> in 97 measurements (95.1%).

## Comparison of P<sub>a</sub>O<sub>2</sub> and P<sub>c</sub>O<sub>2</sub> for P<sub>c</sub>O<sub>2</sub> values ≤55 mmHg (secondary outcome)

The mean difference between gold-standard P<sub>a</sub>O<sub>2</sub> and P<sub>c</sub>O<sub>2</sub> when P<sub>c</sub>O<sub>2</sub> values were ≤55 mmHg was 5.33±5.52 mmHg, with an LLA of -5.48 mmHg (95% CI -7.69 to -3.27 mmHg) and an ULA of 16.15 mmHg (95% CI 13.94 to 18.36 mmHg), Table 3; Figure 2.

**Table 1** Demographic data, ABG, and lung function parameters

N=102	Median	Min	Max	IQR
Male/female (n)	51/51 (50%)			
Age (years)	67.5	44	84	62–73
PY (years) <sup>a</sup>	50.0	0.0	160.0	35.0–65.0
BMI (kg/m <sup>2</sup> )	25.5	13.7	57.3	21.4–31.0
<sub>a</sub> pH	7.43	7.31	7.53	7.40–7.45
P <sub>a</sub> CO <sub>2</sub> (mmHg)	45.9	31.5	85.8	41.6–52.1
<sub>a</sub> HCO <sub>3</sub> <sup>-</sup> (mmol/L)	28.5	20.8	46.3	26.7–30.6
<sub>a</sub> O <sub>2</sub> <sup>b</sup> (%)	89.1	67.9	98.3	85.6–91.4
<sub>p</sub> O <sub>2</sub> <sup>b</sup> (%)	88.0	72.0	94.0	85.0–90.0
FEV <sub>1</sub> (%)	30	10	62	23–37
FEV <sub>1</sub> (L)	0.76	0.31	1.89	0.61–0.94
FEV <sub>1</sub> /IVC (%)	48	23	69	41–56
TLC (%) <sup>c</sup>	113	45	210	93–124
TLC (L) <sup>c</sup>	6.17	2.68	13.18	5.25–7.57
RV (%) <sup>d</sup>	204	54	506	158–247
KCO (%) <sup>e</sup>	59	13	133	42–84
TLCO (%) <sup>e</sup>	36	5	79	28–48

**Notes:** <sup>a</sup>n=98; <sup>b</sup>n=100; <sup>c</sup>n=87; <sup>d</sup>n=86; <sup>e</sup>n=43.

**Abbreviations:** ABG, arterial blood gas analysis; <sub>a</sub>HCO<sub>3</sub><sup>-</sup>, arterial standard bicarbonate; BMI, body mass index; <sub>a</sub>pH, arterial pH; DLCO, diffusing capacity of the lung for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 s; IQR, interquartile range; IVC, inspiratory vital capacity; KCO, transfer coefficient of the lung for carbon monoxide (= Krogh factor); P<sub>a</sub>CO<sub>2</sub>, partial pressure of arterial carbon dioxide; PY, pack years; RV, residual volume; <sub>a</sub>O<sub>2</sub>, arterial oxygen saturation; <sub>p</sub>O<sub>2</sub>, peripheral oxygen saturation; TLC, total lung capacity; TLCO, transfer factor of the lung for carbon monoxide.

**Table 2** Comparison of  $P_aO_2$  and  $P_cO_2$  in all patients (primary outcome)

n	Measurement 1			Measurement 2			Difference		LOA (95% CI)	
	Variable	Mean	SD	Variable	Mean	SD	Mean	SD	Lower	Upper
102	$P_aO_2$	56.28	9.08	$P_cO_2$	50.29	5.94	5.99	6.05	-5.88 (-7.92 to -3.84)	17.85 (15.81 to 19.89)

**Note:** All values are expressed in mmHg.

**Abbreviations:** LOA, limits of agreement;  $P_aO_2$ , partial pressure of arterial oxygen;  $P_cO_2$ , partial pressure of capillary oxygen.

Comparison of other blood gas and peripheral saturation parameters for  $P_cO_2$  values  $\leq 60$  mmHg, as well as for  $P_cO_2$  values  $\leq 55$  mmHg, is displayed in Tables 3 and 4.

Comparison of  $P_aO_2$  and  $P_cO_2$  with respect to the cut-off value of  $P_aO_2 \leq 55$  mmHg (classic indication criteria for LTOT prescription) is displayed in Table 5.

## Assessment of pain associated with blood gas analyses

On the basis of the 100-mm pain VAS, ABG was rated as significantly more painful than CBG ( $P$ -value  $< 0.0001$ ), the mean difference was 9.88 mm ( $\pm 21.06$  mm, 95% CI 5.75–14.02 mm), Table 6.

## Discussion

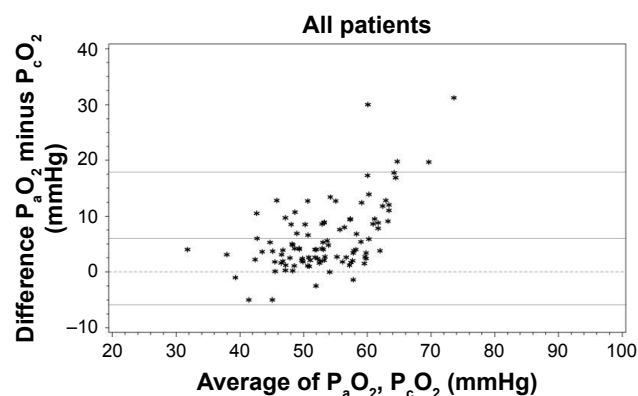
This is the first trial to specifically compare ABG and CBG measurements of  $PO_2$  in hypoxemic COPD patients. Bland–Altman comparison showed wide LOA for  $P_cO_2$  values  $\leq 60$  mmHg (LLA  $-5.88$  mmHg, ULA 17.85 mmHg). Therefore, the main result of the present study was that in hypoxemic COPD patients,  $PO_2$  values derived from CBG do not show an acceptable agreement with those derived from gold-standard ABG. Hereby,  $P_cO_2$  underestimated  $P_aO_2$  by a mean of 6 mmHg. Although the study did not reach the originally planned sample size of 220 patients, analysis of the first 102 patients showed that even with a larger sample size,

proof of agreement with limits between  $-8$  and  $8$  mmHg would not have been possible.

Despite there being no other study that has explicitly evaluated the agreement between ABG and CBG in the context of hypoxemia, subgroup analyses from older studies can be consulted for comparison to the current results. In 1994, Pitkin et al showed close agreement between CBG and ABG, with  $P_cO_2$  underestimating  $P_aO_2$  by a mean of just 1.28 mmHg (LOA  $-8.18$  to 5.62 mmHg).<sup>7</sup> The authors emphasized the particularly good CBG/ABG correlation at  $P_aO_2$  values  $< 60$  mmHg, albeit without providing any further information.<sup>7</sup> Also, only 40 patients were included in the study, with the absolute number of hypoxemic patients included being rather small.<sup>7</sup> Interestingly, the German recommendation for using CBG to indicate LTOT is based solely on this trial.<sup>11,12</sup>

In 2001, Eaton et al also performed a Bland–Altman analysis of CBG versus ABG in patients undergoing assessment for potential LTOT; the mean  $P_aO_2$  here was 63.0 mmHg (range 37.5–84.8 mmHg).<sup>8</sup> Large LOA of  $-15.4$  to 8.2 mmHg were found, where  $P_cO_2$  underestimated  $P_aO_2$  by a mean of 3.6 mmHg.<sup>8</sup> Although these results are in line with the current measurements, it should be noted that only 9 of the 64 measurements were within the range of  $PO_2 < 54.8$  mmHg.<sup>8</sup> No further information about the number of measurements in the range of  $PO_2 < 60$  mmHg was provided.<sup>8</sup>

The 2007 meta-analysis by Zavorsky et al included a subgroup analysis of  $P_aO_2$  values  $< 70$  mmHg,<sup>2</sup> where the mean difference between  $P_aO_2$  and  $P_cO_2$  in 227 measurement pairs was 0.7 mmHg and the SE 0.2 mmHg.<sup>2</sup>  $P_cO_2$  was also shown to be more accurate in predicting  $P_aO_2$  for lower  $PO_2$  values. In contrast, for  $P_aO_2$  values  $\geq 120$  mmHg, the mean difference between  $P_aO_2$  and  $P_cO_2$  was 20 mmHg (SD  $\pm 5.7$  mmHg, SE 4.0 mmHg).<sup>2</sup> This effect had been attributed by the authors to a reduced arteriovenous  $PO_2$  difference in hypoxemia.<sup>2,18</sup> It was also mentioned that the improved accuracy observed in the range of hypoxemic values might be due to the fact that the oxyhemoglobin dissociation curve becomes more linear when  $PO_2$  values range from 20 to 60 mmHg.<sup>2</sup> However, the authors showed that the differences between  $P_cO_2$  and  $P_aO_2$  increased with the year of publication. They suggested



**Figure 1** Bland–Altman comparison of  $P_aO_2$  and  $P_cO_2$  for  $P_cO_2$  values  $\leq 60$  mmHg (primary outcome,  $n=102$ ).

**Abbreviations:**  $P_aO_2$ , partial pressure of arterial oxygen (in mmHg);  $P_cO_2$ , partial pressure of capillary oxygen.

**Table 3** Comparison of blood gas measurements and peripheral saturation measurements for P<sub>c</sub>O<sub>2</sub> ≤55 mmHg (secondary outcome)

n	Measurement 1			Measurement 2			Difference		LOA (95% CI)	
	Variable	Mean	SD	Variable	Mean	SD	Mean	SD	Lower	Upper
73	P <sub>a</sub> O <sub>2</sub>	52.88	7.34	P <sub>c</sub> O <sub>2</sub>	47.55	4.69	5.33	5.52	-5.48 (-7.69 to -3.27)	16.15 (13.94 to 18.36)
73	P <sub>a</sub> CO <sub>2</sub>	47.90	7.61	P <sub>c</sub> CO <sub>2</sub>	49.06	7.59	-1.16	4.06	-9.11 (-10.73 to -7.48)	6.79 (5.17 to 8.42)
73	pH	7.43	0.04	pH	7.43	0.04	0.00	0.02	-0.04 (-0.05 to -0.03)	0.04 (0.03 to 0.05)
73	HCO <sub>3</sub> <sup>-</sup>	29.75	4.00	HCO <sub>3</sub> <sup>-</sup>	30.06	4.05	-0.31	0.69	-1.65 (-1.93 to -1.38)	1.04 (0.76 to 1.31)
72	S <sub>a</sub> O <sub>2</sub>	86.73	5.11	S <sub>c</sub> O <sub>2</sub>	85.27	4.86	1.47	6.63	-5.65 (-7.12 to -4.19)	8.58 (7.12 to 10.05)
72	S <sub>a</sub> O <sub>2</sub>	86.73	5.11	S <sub>p</sub> O <sub>2</sub>	86.25	3.97	0.48	2.87	-5.14 (-6.29 to -3.98)	6.10 (4.94 to 7.25)
72	S <sub>p</sub> O <sub>2</sub>	86.25	3.97	S <sub>c</sub> O <sub>2</sub>	85.27	4.86	0.98	2.77	-4.44 (-5.55 to -3.32)	6.40 (5.29 to 7.52)

**Note:** All values are expressed in mmHg.

**Abbreviations:** pH, arterial pH; HCO<sub>3</sub><sup>-</sup>, arterial standard bicarbonate; HCO<sub>3</sub><sup>-</sup>, capillary standard bicarbonate; pH, capillary pH; LOA, limits of agreement; P<sub>a</sub>CO<sub>2</sub>, partial pressure of arterial carbon dioxide; P<sub>c</sub>CO<sub>2</sub>, partial pressure of capillary carbon dioxide; P<sub>a</sub>O<sub>2</sub>, partial pressure of arterial oxygen; P<sub>c</sub>O<sub>2</sub>, partial pressure of capillary oxygen; S<sub>a</sub>O<sub>2</sub>, arterial oxygen saturation; S<sub>c</sub>O<sub>2</sub>, capillary oxygen saturation; S<sub>p</sub>O<sub>2</sub>, peripheral oxygen saturation.

that this might be due to either a submission or a publication bias in early studies, whereby only positive trials with good levels of accuracy between ABG and CBG were submitted by authors or published by the journals, respectively.<sup>2</sup>

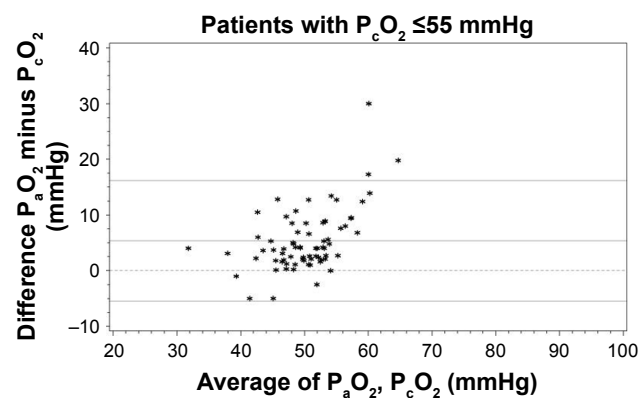
The most recent comparison of ABG and CBG by Ekkernkamp et al<sup>9</sup> reported a mean difference between P<sub>a</sub>O<sub>2</sub> and P<sub>c</sub>O<sub>2</sub> of 5.6 mmHg (SD ±7.2 mmHg), again with wide LOA (-8.5 to 19.6 mmHg). The mean P<sub>a</sub>O<sub>2</sub> was 80.4 mmHg (SD ±17.7 mmHg). An additional analysis of this study in the subgroup of patients with P<sub>a</sub>O<sub>2</sub> values <60 mmHg showed a mean difference of -1.3 mmHg (SD ±3.4), but only 7/100 measurements had P<sub>a</sub>O<sub>2</sub> values <60 mmHg (data not published). Therefore, this has to be interpreted with caution. Nevertheless, the overall agreement between P<sub>c</sub>O<sub>2</sub> and P<sub>a</sub>O<sub>2</sub> in the Ekkernkamp trial as well as in the current trial was lower than that reported in the meta-analysis, in line with the finding that older studies showed better agreement between CBG and ABG than more recent trials.<sup>2,9</sup>

If CBG combined with a P<sub>a</sub>O<sub>2</sub> cut-off value of ≤55 mmHg had been used for the evaluation of LTOT in our cohort,

21 of 73 patients (28.8%) would have been prescribed LTOT unnecessarily. If a P<sub>a</sub>O<sub>2</sub> <60 mmHg had been used as the cut-off value (in patients with the presence of secondary polycythemia and/or signs of right heart insufficiency/pulmonary hypertension),<sup>10,11</sup> 31 of 102 patients (30.4%) would have been prescribed LTOT unnecessarily. However, none of the patients would have been unnecessarily denied LTOT if CBG were used for the evaluation of LTOT, and this was true for both cut-off values. This is in line with the study by Eaton et al<sup>8</sup> which reported that, using CBG alone to assess the need for LTOT (cutoff criteria PO<sub>2</sub> ≤55 mmHg) would have resulted in 16% (9/55 patients) of the patients receiving LTOT unnecessarily, while no patient would have been incorrectly denied LTOT.<sup>8</sup>

LTOT has only been shown to improve survival in severe hypoxemic patients who meet the classic indication criteria.<sup>19,20</sup> In addition, LTOT is an expensive therapy associated with psychosocial side effects such as depression, fear of dependence, lack of self-confidence, and social isolation.<sup>21-24</sup> Therefore, overprescription of this treatment should be strictly avoided. Taken together, there is now increasing evidence to suggest that assessing the requirement for LTOT should never be based on CBG measurements alone. This has already been incorporated into the recent BTS guideline for LTOT.<sup>10</sup>

In general, P<sub>c</sub>O<sub>2</sub> should be lower than P<sub>a</sub>O<sub>2</sub> due to the facts that 1) the skin capillary bed consumes oxygen and 2) the blood drawn from the earlobe is a mixture of capillary and venous blood.<sup>2</sup> Therefore, a sufficient vasodilatation (by either heat or a vasoactive ointment) to ensure a sufficient earlobe blood flow relative to oxygen consumption is needed to obtain close agreement between P<sub>c</sub>O<sub>2</sub> and P<sub>a</sub>O<sub>2</sub>.<sup>2</sup> Hence, one possible explanation for the poor agreement between PO<sub>2</sub> values in our cohort despite the fact that the agreement is supposed to be more accurate in hypoxemic PO<sub>2</sub> values (see above) could



**Figure 2** Bland-Altman comparison of P<sub>a</sub>O<sub>2</sub> and P<sub>c</sub>O<sub>2</sub> for P<sub>c</sub>O<sub>2</sub> values ≤55 mmHg (secondary outcome, n=73).

**Abbreviations:** P<sub>a</sub>O<sub>2</sub>, partial pressure of arterial oxygen (in mmHg); P<sub>c</sub>O<sub>2</sub>, partial pressure of capillary oxygen.

**Table 4** Comparison of blood gas measurements and peripheral saturation measurements in all patients (secondary outcome)

n	Measurement 1			Measurement 2			Difference		LOA (95%CI)	
	Variable	Mean	SD	Variable	Mean	SD	Mean	SD	Lower	Upper
102	P <sub>a</sub> CO <sub>2</sub>	47.04	8.32	P <sub>c</sub> CO <sub>2</sub>	48.01	8.23	-0.97	3.75	-8.31 (-9.5 to -7.05)	6.37 (5.11 to 7.63)
102	pH	7.43	0.04	pH	7.43	0.04	0.00	0.02	-0.04 (-0.05 to -0.03)	0.04 (0.03 to 0.05)
102	HCO <sub>3</sub> <sup>-</sup>	29.22	3.82	HCO <sub>3</sub> <sup>-</sup>	29.52	3.86	-0.30	0.70	-1.67 (-1.91 to -1.43)	1.08 (0.84 to 1.31)
100	S <sub>a</sub> O <sub>2</sub>	88.29	5.13	S <sub>c</sub> O <sub>2</sub>	87.00	5.03	1.29	3.27	-5.11 (-6.22 to -4.00)	7.69 (6.58 to 8.80)
100	S <sub>a</sub> O <sub>2</sub>	88.29	5.13	S <sub>p</sub> O <sub>2</sub>	87.33	3.93	0.96	2.67	-4.28 (-5.19 to -3.37)	6.20 (5.29 to 7.11)
100	S <sub>p</sub> O <sub>2</sub>	87.33	3.93	S <sub>c</sub> O <sub>2</sub>	87.00	5.03	0.33	2.73	-5.02 (-5.95 to -4.09)	5.68 (4.75 to 6.61)

**Note:** All values are expressed in mmHg.

**Abbreviations:** HCO<sub>3</sub><sup>-</sup>, arterial standard bicarbonate; pH, arterial pH; HCO<sub>3</sub><sup>-</sup>, capillary standard bicarbonate; pH, capillary pH; LOA, limits of agreement; P<sub>a</sub>CO<sub>2</sub>, partial pressure of arterial carbon dioxide; P<sub>c</sub>CO<sub>2</sub>, partial pressure of capillary carbon dioxide; S<sub>a</sub>O<sub>2</sub>, arterial oxygen saturation; S<sub>c</sub>O<sub>2</sub>, capillary oxygen saturation; S<sub>p</sub>O<sub>2</sub>, peripheral oxygen saturation.

be that not all of the patients responded well to the vasodilatory ointment used to heat the earlobe. A way to quantify this would be to measure the surface temperature of the earlobe prior to puncture. It might also be possible that certain formulas of vasodilatory ointment might work better than others. Interestingly, all trials used slightly different ointments.<sup>7-9</sup> Therefore, future trials should focus on this issue. Another explanation for the poor agreement could be the abovementioned publication bias that was reported by Zavorsky et al and is also confirmed by the latest trial by Ekkernkamp et al, which also showed worse agreement than older trials.<sup>2,9</sup>

The current cohort of advanced COPD patients reported an overall moderate level of pain with both techniques. However, ABG was rated as significantly more painful than CBG, although a very fine needle (27 G) was used in this trial. Older trials using much thicker needles (22–23 G) have previously shown that patients experience more discomfort with ABGs compared with CBGs.<sup>5,8</sup> In contrast, a recently published trial which also used a very fine needle (26 G) showed that ABGs were subjectively less painful than CBGs, although this result might have been biased due to double sampling of CBG for each patient (compared to one ABG analysis).<sup>9</sup>

These conflicting results could be explained by the fact that whereas all of our patients were used to CBGs due to their underlying diagnosis of COPD, not all of them had previously undergone ABGs. Therefore, the technique with which the patient is more familiar (in this case, CBG) is more likely to be rated as less painful.

**Table 5** Comparison of P<sub>a</sub>O<sub>2</sub> and P<sub>c</sub>O<sub>2</sub> with respect to P<sub>c</sub>O<sub>2</sub>-based indication of LTOT

	P <sub>a</sub> O <sub>2</sub> ≤55 mmHg (n=52)	P <sub>a</sub> O <sub>2</sub> >55 mmHg (n=50)
P <sub>c</sub> O <sub>2</sub> ≤55 mmHg (n=73)	52 (51.0%)	21 (20.6%)
P <sub>c</sub> O <sub>2</sub> >55 mmHg (n=29)	0 (0%)	29 (28.4%)

**Abbreviations:** P<sub>a</sub>O<sub>2</sub>, partial pressure of arterial oxygen; P<sub>c</sub>O<sub>2</sub>, partial pressure of capillary oxygen.

ABGs in the current trial were judged to be almost as painful as the ABGs carried out in the Ekkernkamp trial,<sup>9</sup> while CBGs were considered to be much less painful in the present trial compared with the Ekkernkamp trial.<sup>9</sup> The discrepancy between these findings might be explained by the fact that all of our patients were used to CBGs while at least 20% of the patients in the Ekkernkamp trial might not have been used to frequent blood gas analysis because they were either healthy volunteers or had diagnoses that do not necessarily require frequent CBGs (eg, sleep apnea syndrome).<sup>9</sup>

One limitation of the study was that the calculated sample size of 220 patients could not be reached due to recruitment issues. Nevertheless, the statistical analysis showed wide LOA between P<sub>a</sub>O<sub>2</sub> and P<sub>c</sub>O<sub>2</sub>, indicating that the predicted sample size would not have resulted in better agreement between the two techniques.

Since all of our measurements were performed in COPD patients, the results are not directly applicable to other hypoxic patients, although it is unlikely that one specific disease would lead to a worse CBG performance. Nevertheless, future trials should address this issue.

## Conclusion

P<sub>c</sub>O<sub>2</sub> did not adequately reflect P<sub>a</sub>O<sub>2</sub> in this study, as demonstrated by the wide LOA. In fact, it was shown that a significant number of patients in this cohort would have been overprescribed LTOT if based on CBG, although patients did not meet the classic indication criteria based on ABG. ABG

**Table 6** Assessment of pain associated with blood gas analyses

n=102	Mean	Min	Max	SD
ABG <sub>VAS</sub>	23.86	0	86.0	22.72
CBG <sub>VAS</sub>	13.98	0	70.0	16.19

**Abbreviations:** ABG<sub>VAS</sub>, pain (rated on the 100-mm visual analog scale) associated with arterial blood gas analysis; CBG<sub>VAS</sub>, pain associated with capillary blood gas analysis (on 100-mm visual analog scale); max, maximum value; min, minimum value.

was rated to be more painful than CBG, but overall the level of pain sensation was moderate.

Therefore, based on the current and recent evidence,<sup>9,10</sup> the present authors suggest that the indication for LTOT should be based on ABG, rather than CBG alone.

## Acknowledgments

We acknowledge all participants for the effort they devoted to this study and Dr Sandra Dieni for proofreading the manuscript.

The Cologne study group (FSM, SBS, JC, JHS, and WW) received an open research grant from Weinmann/Germany, Vivisol/Germany, Heinen und Löwenstein/Germany, and VitalAire/Germany.

## Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

FSM, JC, JHS, and SBS received personal travel grants from companies dealing with LTOT. WW and JHS received speaking fees from companies dealing with LTOT. The authors report no other conflicts of interest in this work.

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