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Diffusion Limitations of the Lung – Comparison of Different Measurement Methods

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In every breath we breathe two graces share – The indraught and the outflow of the air; that is a toil, but this refreshment brings; So marvellous are our life's comminglings. (Johann Wolfgang von Goethe 1819)

Abstract

Pulmonary fibrosis leads to a decrease of oxygen diffusion, in particular during exercise. Bronchial obstruction also could decrease the partial pressure of oxygen (P_aO_2). In this study we investigated the validity of blood gas content, especially P_aO_2 and P_aO_2 affected by hyperventilation (P_aO_{2corr}) and alveolo-arterial oxygen gradient ($P_{A\text{-}a}O_2$) in comparison with the CO diffusion capacity (DL_{CO}) in different lung diseases. A total of 250 subjects were studied (52.3 ± 12.5 year; F/M 40/210), among which there were 162 subjects with different lung disorders and 88 healthy controls. Pearson's correlation coefficients (r) of DL_{CO} with P_aO_2, P_aO_{2corr}, and $P_{A\text{-}a}O_2$ were analyzed in each group. The results show that the diagnostic power of $P_{A\text{-}a}O_2$ against P_aO_{2corr} was equivalent, especially during exercise ($r = -0.89$ and -0.92, respectively). DL_{CO} showed only weak correlations with P_aO_{2corr} and $P_{A\text{-}a}O_2$ ($r = 0.17$ and -0.19, respectively). In conclusion, DL_{CO} shows a better match with blood gas content during exercise than at rest during which it is routinely tested. Thus, the exercise test is advisable. The $P_{A\text{-}a}O_2$ takes into account the level of ventilation, which makes it correlate better with DL_{CO} rather than with blood gas content. The most significant problems in clinical evaluation of blood gas parameters during exercise are the insufficiently defined limits of normal-to-pathological range.

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Keywords
Gas diffusion • Lung • Blood gas content • Cardiopulmonary exercise testing • Oxygen uptake • Alveolar arterial oxygen gradient • Hyperventilation

1 Introduction

Basic prerequisite of any organism is the oxygen supply to all its cells. The central organ of gas transportation is the lung and the blood is a carrier. Oxygenation is achieved by the ventilatory gas exchange and diffusion of gases through the alveolar and capillary walls. The measurement and determination of gas exchange in the lung is therefore a key requirement in the diagnosis of vital functions, especially in obstructive and restrictive lung diseases.

Commonly used is the measurement of the diffusing capacity for CO (DL_{CO}); CO diffusion having the characteristics similar to those of O_2 diffusion. An alternative is a measurement of the results of gas exchange, namely the content of O_2 and CO_2 in arterial or arterialized capillary blood. The diffusion capacity of the lung for gas represents an integral of respiratory function since ventilation, diffusion, and perfusion are included in the measurement.

In general, restrictive lung disease, like fibrosis, results in decreases of oxygen diffusion and arterial oxygen partial pressure (P_aO_2), especially during exercise, compared with obstructive airway diseases which are often associated with a mismatch of ventilation and perfusion. Although both diseases show the key symptom of dyspnea, the cause of dyspnea may be diverse.

Both hyperventilation and hypoventilation affect the pulmonary uptake of O_2 and consequently the P_aO_2: hyperventilation leads to an increase of P_aO_2, so that a malfunction of gas exchange may be underestimated. Therefore, determination of diffusion characteristics through blood gas analysis should take into account the level of ventilation. This integration of ventilation in the assessment of blood gases is enabled by determining the alveolar-arterial oxygen difference ($P_{A\text{-}a}O_2$). It requires not only the measurement of blood gas content but also of the breathing gases O_2 and CO_2 by means of a complex technique. This methodology is always part of a cardiopulmonary exercise testing (CPX).

Another way to calculate the influence of hyperventilation on the P_aO_2 is to assess a decrease in the arterial partial pressure of carbon dioxide (P_aCO_2). The P_aCO_2 is here used to quantify the influence of ventilation; the P_aO_2 can thus be 'corrected' according to the formula: $P_aO_{2corr} = P_aO_2 - 1.66 \times (40\text{-}P_aCO_2)$ (Diekmann and Smidt 1984). The mathematical correction of P_aO_2 is much simpler to perform than the determination of the $P_{A\text{-}a}O_2$. The question arises whether the results of these two measurements are equivalent. Therefore, in the present study we investigated the validity of P_aO_2, P_aO_{2corr}, and $P_{A\text{-}a}O_2$ – all in comparison to DL_{CO} in various lung diseases.

2 Methods

2.1 Participants

The participants were recruited in our occupational outpatient clinic over a period of 5 years and all of them gave signed written consent to use their samples and data. The study was approved by the Internal Medical Review Board. They presented themselves for the diagnosis of work-related diseases and occupational medical examinations. A total of 250 subjects (mean age 52.3 ± 12.5 year; F/M 40/210) were eligible and consecutively included after they had performed CPX with blood gas analysis, DL_{CO}, or both as part of their routine investigation. In addition, medical history, physical examination, spirometry, and body plethysmography were taken in all subjects. We excluded 10 cases due to single missing values. From the remaining

240 individuals, there were: 13 with restrictive lung disorder, defined as VC < lower limit of normal (LLN) (with normal FEV_1/VC, DL_{CO} normal or reduced); 19 with normal VC but DL_{CO} < LLN; 86 with mild or moderate bronchial obstruction (FEV_1/VC < LLN, VC > LLN), 34 subjects with a mixed obstructive/restrictive lung disorder (FEV_1/VC < LLN, VC < LLN), and 88 healthy controls without past or present pulmonary disorders and with normal lung function results. The examinations were performed as part of routine social security screening.

2.2 Lung Function Tests

Lung function and CPX tests were carried out according to the quality criteria of the European Respiratory Society (ERS) and the American Thoracic Society (ATS) (Meyer et al. 2013; Macintyre et al. 2005; Miller et al. 2005; American Thoracic Society 2003). Blood gas analysis at rest was based on the target values of Woitowitz et al. (1969) and the DL_{CO} on those of Cotes et al. (1993). The P_aO_2 during exercise was deemed pathological if it fell below the predicted value by ≥5 mmHg (Meyer et al. 2013). The $P_{A\text{-}a}O_2$ was calculated at rest and under load from the measured values of CPX using the formula: $P_AO_2 = FiO_2 \bullet 713 - (P_ACO_2/$ respiratory exchange rate (RER)) (Riley and Cournand 1949). A pathological increase was assumed at a value of >20 mmHg at rest and >35 mmHg during exercise (Meyer et al. 2013; American Thoracic Society 2003).

2.3 Statistical Analysis

Pearson's correlation coefficient (r) was analyzed for DL_{CO} with P_aO_2, DL_{CO} with P_aO_2 after correction of ventilation and DL_{CO} with $P_{A\text{-}a}O_2$, all measured at rest and under load. Correlations of blood gas-dependent parameters (P_aO_2, P_aO_{2corr}, and $P_{A\text{-}a}O_2$) were determined with each other; all calculations were carried out separately for each group of lung diseases.

Cohen's kappa coefficient (Grouven et al. 2007; Thompson and Walter 1988) was calculated to assess the conformity of the values measured with different methods; where '1' indicates a full match, '0' indicates a purely random coincidence, and negative values represent an even lower than a random match. Crosstabs were made to compare the quality of different measurement methods (healthy/pathological assessments). In 39 male subjects, DL_{CO} values were evaluated as based on the level of current hemoglobin concentration corrected (Mottram et al. 1999) and compared with the DL_{CO} of the total cohort. All correlations were calculated according to Pearson (1909), as all variables were interval scaled and normally distributed. Statistical analysis was performed with a commercial SPSS package ver. 19 and 20.

3 Results

The DL_{CO} value (% predicted value) showed in the total cohort only a low correlation of 0.25 ($p < 0.001$) to P_aO_2 at rest and a moderate correlation of 0.57 ($p < 0.001$) to P_aO_2 during exercise (Fig. 1a, b, Table 1). The measurement of $P_{A\text{-}a}O_2$ under load, which takes into account ventilation, showed only a moderate correlation with DL_{CO} of −0.47 ($p < 0.001$) in the total cohort. This correlation remained at a similar level of 0.44 for the 'corrected' P_aO_2 that takes into account P_aCO_2 (Table 1). Higher correlations were found in the first two groups of restrictive lung disease (corresponding with reduced VC or normal VC, but reduced DL_{CO}). Poor correlations in the group with normal lung function values ('healthy lung') can be explained by the closely adjacent individual values (see dense point clouds of this group in Fig. 1a, b).

The P_aO_2 and $P_{A\text{-}a}O_2$ highly correlated with each other at rest and also under load ($r = -0.83$, $r = -0.83$, respectively), which was particularly evident comparing the P_aO_{2corr} and $P_{A\text{-}a}O_2$ with respect to the ventilation values ($r = -0.89$, $r = -0.92$, respectively) (Fig. 2a, b, Table 2). Such high correlations were confirmed by differentiated calculations using crosstabs and kappa values. Kappa values and crosstabs showed a strong concordance, especially under load ($\kappa = 0.69$), particularly within the group of

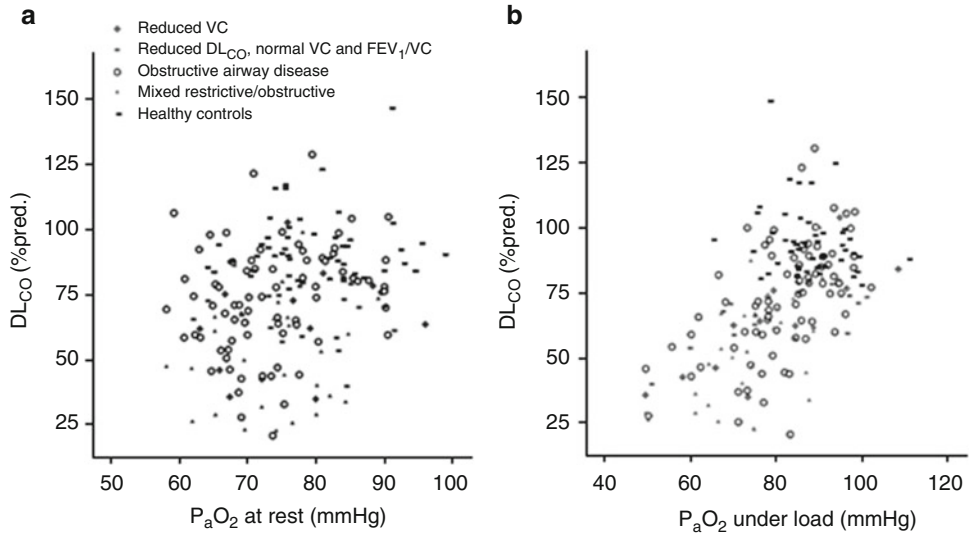

Fig. 1 Correlation between DL_{CO} (%pred.) and P_aO_2 at rest (**a**) and under exercise load (**b**)

Table 1 Correlation coefficients (r) of DL_{CO} with P_aO_2 at rest and P_aO_2 under load, and with $P_{A\text{-}a}O_2$ and P_aO_{2corr} under load

	n	DL_{CO}–P_aO_2 at rest	DL_{CO}–P_aO_2 under load	DL_{CO}–$P_{A\text{-}a}O_2$ under load	DL_{CO}–P_aO_{2corr} under load
All	240	0.25***	0.57***	−0.47***	0.44***
Restrictive lung disease	13	0.30	0.82***	−0.84***	0.74**
Decreased DL_{CO}, normal VC	19	−0.17	0.68**	−0.64**	0.58*
Obstructive airway disease	86	0.24*	0.55***	−0.47***	0.51***
Mixed restrictive/obstructive	34	0.01	0.58***	−0.41*	0.30
Unobtrusive lung function	88	0.09	−0.23	0.19	−0.34*

*p < 0.05, **p < 0.01, ***p < 0.001

restrictive lung disease ($r = -0.95$, $\kappa = 0.68$). Therefore, $P_{A\text{-}a}O_2$ offers no diagnostic advantage over the corrected P_aO_2 (Table 3), wherein this consideration is essentially dependent on the underlying limits of normal.

When not using the specified correction for load of minus 5 mmHg for the lower limit of P_aO_2 (Meyer et al. 2013), a full match ($\kappa = 1.0$) of the crosstabs for the $P_{A\text{-}a}O_2$ compared with P_aO_{2corr} was present in the group of restrictive lung disease (data not shown). The crosstabs and kappa values for the blood-gas dependent parameters at rest (P_aO_{2corr} and $P_{A\text{-}a}O_2$) with the DL_{CO} showed weak correlations (DL_{CO} and P_aO_{2corr}: $r = 0.17$, $\kappa = 0.10$; DL_{CO} and $P_{A\text{-}a}O_2$: $r = -0.19$, $\kappa = 0.06$) in the total cohort.

Blood gas levels in combination with their corresponding parameters from the exercise test showed a moderate correlation to DL_{CO} and – according to the kappa value – low dependence in the clinical assessment (DL_{CO} and P_aO_{2corr} under load: $r = 0.44$, $\kappa = 0.22$; DL_{CO} and $P_{A\text{-}a}O_2$ under load: $r = -0.47$, $\kappa = 0.23$, see Table 4). Similarities were mainly in the group of persons with restrictive lung disease; even there, significant correlations were present when

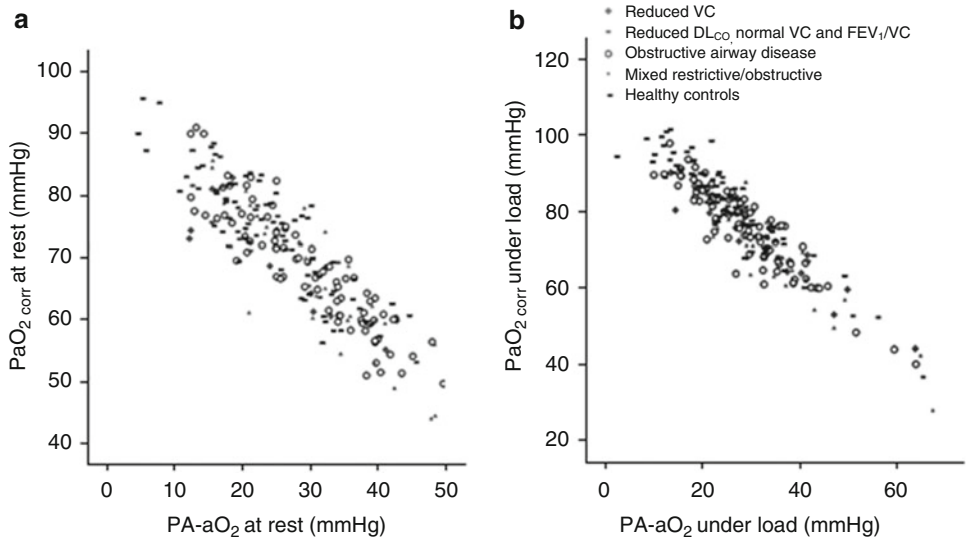

Fig. 2 Correlation of P_aO_{2corr} and $P_{A\text{-}a}O_2$ at rest (**a**) and under exercise load (**b**)

Table 2 Correlation coefficients (r) of $P_{A\text{-}a}O_2$ with P_aO_{2corr} at rest and under load

	n	$P_{A\text{-}a}O_2$–P_aO_{2corr} at rest	$P_{A\text{-}a}O_2$–P_aO_{2corr} under load
All	240	−0.89***	−0.92***
Restrictive lung disease	13	−0.85***	−0.95***
Decreased DL_{CO}, normal VC	19	−0.86***	−0.98***
Obstructive airway disease	86	−0.91***	−0.91***
Mixed restrictive/obstructive	34	−0.90***	−0.91***
Unobtrusive lung function	88	−0.87***	−0.90***

***$p < 0.001$

Table 3 Kappa values (κ) for comparison of $P_aO_{2corr\ with}$ $P_{A\text{-}a}O_2$ under load: **A** – in the total cohort and **B** – in the restrictive lung disease group

A		$P_{A\text{-}a}O_2$ under load		
P_aO_{2corr} under load		Pathological (>35 mmHg)	Normal	Total
	Pathological (<LLN–5 mmHg)	35	7	42
	Normal	16	169	185
	Total	51	176	227[a]
$\kappa = 0.69$				
B		$P_{A\text{-}a}O_2$ under load		
P_aO_{2corr} under load		Pathological (>35 mmHg)	Normal	Total
	Pathological (<LLN–5 mmHg)	4	2	6
	Normal	0	7	7
	Total	4	9	13
$\kappa = 0.68$				

[a]For 13 subjects, there were no values at exercise, therefore they are not rated, this implies the difference to 240

Table 4 Kappa values (κ) for comparison of DL_{CO} at rest with: **A** – P_aO_{2corr} under load and **B** – $P_{a\text{-}a}O_2$ under load

A		DL_{CO} at rest		
P_aO_{2corr} under load		Pathological (<LLN)	Normal	Total
	Pathological (<LLN–5 mmHg)	31	9	40
	Normal	66	82	148
	Total	97	91	188[a]
$\kappa = 0.22$				
B		DL_{CO} at rest		
$P_{A\text{-}a}O_2$ under load		Pathological (<LLN)	Normal	Total
	Pathological (>35 mmHg)	36	13	49
	Normal	61	78	139
	Total	97	91	188[a]
$\kappa = 0.23$				

[a]For 52 subjects there were no values for DL_{CO} or exercise test, this implies the difference to 240

the blood gas-dependent values were obtained under load (DL_{CO}–P_aO_{2corr} load: $r = 0.74$, $\kappa = 0.24$; DL_{CO}–$P_{A\text{-}a}O_2$ under load: $r = -0.84$, $\kappa = 0.41$). In the other groups (obstructive airways disease; mixed restrictive/obstructive disorders; unobtrusive lung function), the similarities were rather weak (data not shown).

As a supplement, the difference between the DL_{CO} value corrected to the current level of hemoglobin and the otherwise underlying DL_{CO} value was calculated in 39 male patients (with assumption of a hemoglobin level of 14.6 g/dL). There was a small deviation in the mean DL_{CO} of 3.0 ± 2.2 %. This outpatient study, with the exclusion of severely ill people, showed the influence of the hemoglobin level to be of little relevance.

4 Discussion

Blood gas analysis and DL_{CO} are the most important diagnostic steps in the assessment of pulmonary gas exchange in routine diagnostics. However, both methods are not always available and their results are affected differently by the respective pulmonary disease and hypo- or hyperventilation. The determination of the alveolar-arterial oxygen difference ($P_{A\text{-}a}O_2$) allows the inclusion of ventilation in the assessment of blood gases. This, in turn, requires not only the blood gas analysis, but also the determination of the exchange of respiratory gases O_2 and CO_2 by means of a complex measuring equipment. Such equipment is part of a cardiopulmonary exercise testing and the method is thus used frequently in the context of cardiopulmonary exercise tests. The influence that ventilation exerts on the P_aO_2 can be assessed by calculating the exhaled CO_2 and thus the 'correction' of P_aO_2 can be made. The P_aCO_2 is used to quantify the influence of ventilation. In practice, the corrected P_aO_2 is attained with the results of blood gas analysis in combination with a simple 'correction formula' (Diekmann and Smidt 1984). Furthermore, we wanted to verify whether the blood gas values allow for the identification of various lung gas exchange disorders, such as – based on an entirely different principle of measurement – determination of diffusion of CO in the lung (DL_{CO}). It should be noted that the DL_{CO} is to be determined only at rest.

The DL_{CO} is a result of two measurements during a single-breath method (Hughes and Pride 2001): the diffusion gradient at the alveolar membrane and the ventilated alveolar volume. Both result from the measurements of volume, gas concentrations, and calculations. The assumption that DL_{CO} correction using the alveolar volume (DL_{CO}/VA) leads to a more accurate determination of lung diffusion capacity cannot be confirmed by recent publications, since the change of the quotient is not constant with the change of alveolar volume (Hughes and Pride

2012). Therefore, just DL_{CO} and not the DL_{CO}/VA ratio was considered in the context of the present work. The DL_{CO} is considered the gold standard to verify lung diffusion disorders, regardless of their genesis. A closer look at our results reveals that this may apply only for restrictive lung diseases, at least in comparison with blood gas analysis, even after correction of ventilation. A decrease in P_aO_2 found in blood gas analysis also points to this disease, but the severity of gas exchange impairment could be underestimated if hyperventilation is not observed. Therefore, the arithmetical correction of ventilation can also be useful here.

In obstructive airway disease, in 45 % of cases, the CO diffusion disorder cannot be confirmed by blood gas analysis and $P_{A\text{-}a}O_2$ during exercise. In our opinion, the DL_{CO} also appears negatively affected by inhomogeneity of ventilation and perfusion resulting in gas exchange disorders even at rest. This inhomogeneity is known, in particular, for obstructive lung diseases. Only exercise tests seem to provide a better differentiation of a fixed diffusion disorder. Schwarz et al. (1999) also concluded that the $P_{A\text{-}a}O_2$ determined by CPX is a more sensitive parameter, compared with P_aO_2, in the evaluation of gas exchange disorders. The authors also found only a weak correlation of DL_{CO} to $P_{A\text{-}a}O_2$. Both parameters would have a better match if one would measure not only P_aO_2, but also DL_{CO} under load. This would counterbalance the ventilation-perfusion inequality. This inhomogeneity in obstructive lung disease appears of less importance in restrictive lung diseases. DL_{CO} measurements in the loading condition would give a truer assessment of the factual gas diffusion – however, this is not yet available. Furthermore, inhomogeneity of lung perfusion and ventilation under load would be reduced and the entire system of gas exchange would be tested at load limit.

At present, DL_{CO} and blood gas content measurements do not provide comparable values enabling their clinical evaluation. To detect malfunctions in the system, the blood gas content under load, determined with a correction of P_aO_2 in rapport with the level of ventilation, has the best explanatory power for clinical assessment. The $P_{A\text{-}a}O_2$ has a similar power, but there are no reliable set point-values, which complicates the clinical evaluation. Thus, $P_{A\text{-}a}O_2$ shows no significant advantage over the P_aO_2. Nevertheless, one should - as also others report (Schwarz et al. 1999) – use the parameters associated with history, clinical, laboratory values, and imaging techniques. Exercise testing enhances the evaluation of severity, prognosis, and treatment monitoring (Meyer et al. 2013).

The collected absolute values – in particular, the blood gas parameters derived there from $P_{A\text{-}a}O_2$ and P_aO_{2corr} – are well comparable and highly correlated, so that the explanatory power of the $P_{A\text{-}a}O_2$ against the P_aO_{2corr} seems diagnostically equivalent. However, given the need to use the CPX system to determine ventilation and $P_{A\text{-}a}O_2$ or the above-mentioned calculations to obtain P_aO_{2corr}, using the P_aCO_2, there is a small advantage compared with the determination of P_aO_2 alone. The main challenge consists of setting a demarcation line between normal and pathological values. This is by far only vaguely defined for $P_{A\text{-}a}O_2$ with a limit of 35 mmHg across all age groups and all load levels. The assessment of blood gases also shows discrepancies. The generally assumed limit of 5 mmHg below the normal value is questioned as it may be age- and exercise-dependent.

For the present study, it is essential to note that X-ray images of the subjects investigated were not always present. It was assumed that relevant changes would be reflected in pathological lung function values. It should also be noted that the maximum workload was not defined and was not included in the analysis. The subjects achieved their individual maximum wattage depending on gender, height, weight, age, fitness level, and an existing lung disease. The increase in wattage per minute was selected depending on the expected overall performance and took place after 8–12 min (Preisser and Ochmann 2011). Accordingly, these factors were highly variable. The aim of the study was to capture the effect of blood circulation and pulmonary ventilation as prominently as possible; therefore, the endpoint of maximum workload was selected.

5 Conclusions

In general, only a few conclusions about the existence of a gas exchange disorder can be drawn from the blood gas analysis at rest. The DL_{CO} also is determined only at rest, but shows a slightly better match with the results of the blood gas content during exercise than that at rest. The exercise testing is thus desirable.

Exercise testing is becoming increasingly important in the evaluation of disease severity, prognosis, and therapy monitoring. The inhomogeneity of perfusion and ventilation, influencing the P_aO_2, can be revealed through the exercise test, not only for obstructive airway diseases but also in healthy subjects (Meyer et al. 2013). The exercise test should include the determination of blood gases, and in the case of cardiopulmonary exercise tests, also the alveolar-arterial oxygen difference. The $P_{A\text{-}a}O_2$ takes into account the level of ventilation, thus it probably has a better correlation with DL_{CO} compared with the blood gas analysis.

In restrictive lung disease, all three parameters are comparably suitable to detect the gas exchange disorder. In obstructive airway disease, DL_{CO} seems affected by other pathophysiological aspects; thus there is only a moderate correlation with the blood gas-based parameters. The blood gas analysis at rest can lead to false-negative results, especially in case of restrictive lung disease. The DL_{CO} indicates more likely false-positive results, especially for obstructive airway diseases.

Changes in $P_{A\text{-}a}O_2$ and P_aO_2 during exercise are highly comparable in patients with restrictive lung disease. An exercise test with the determination of blood gases seems to be diagnostically adequate in these cases, at least for the evaluation of gas exchange disorders.

The 'correction' formula of Diekmann and Smidt (1984) is also applicable for the blood gas content in the exercise load condition, but gives no advantage over the P_aO_2 in the assessment of different lung diseases. However, clinical classification as 'normal' or 'pathological' shows only a moderate difference in $P_{A\text{-}a}O_2$ and in ventilation corrected P_aO_2. The most significant problem in the clinical application of the blood gas parameters at exercise and of $P_{A\text{-}a}O_2$ stems from the lack of clearly defined normal-to- pathological range, in particular, for the $P_{A\text{-}a}O_2$, where validated reference values are needed.

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Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

References

American Thoracic Society (2003) ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 167:211–277

Cotes JE, Chinn DJ, Quanjer PH, Roca J, Yernault JC (1993) Standardization of the measurement of transfer factor (diffusing capacity). Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 16:41–52

Diekmann M, Smidt U (1984) Berechnung eines Standard-PaO_2 in Analogie zum Standard Bikarbonat. Atemwegs-Lungenkrkh 6:248–250

Grouven U, Bender R, Ziegler A, Lange S (2007) The kappa coefficient. Dtsch Med Wochenschr 132(Suppl 1):e65–e68

Hughes JM, Pride NB (2001) In defence of the carbon monoxide transfer coefficient Kco (TL/VA). Eur Respir J 17:168–174

Hughes JM, Pride NB (2012) Examination of the carbon monoxide diffusing capacity (DL_{CO}) in relation to its K_{CO} and VA components. Am J Respir Crit Care Med 186:132–139

Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, Gustafsson P, Hankinson J, Jensen R, McKay R, Miller MR, Navajas D, Pedersen OF, Pellegrino R, Wanger J (2005) Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 26:720–735

Meyer FJ, Borst MM, Buschmann HC, Ewert R, Friedmann-Bette B, Ochmann U, Petermann W, Preisser AM, Rohde D, Ruhle KH, Sorichter S, Stahler G, Westhoff M, Worth H (2013) Exercise testing in respiratory medicine. Pneumologie 67:16–34

Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC,

MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J (2005) Standardisation of spirometry. Eur Respir J 26:319–338

Mottram C, Blonshine S, Brown RA, Ruppel GL, Wanger J (1999) AARC clinical practice guideline: single-breath carbon monoxide diffusing capacity, 1999 update. Respir Care 44:539–546

Pearson K (1909) Determination of the coefficient of correlation. Science 757:23–25

Preisser AM, Ochmann U (2011) Cardiopulmonary exercise testing in occupational medical fitness examination and assessment. Pneumologie 65:662–670

Riley RL, Cournand A (1949) Ideal alveolar air and the analysis of ventilation-perfusion relationships in the lungs. J Appl Physiol 1:825–847

Schwarz S, Kaukel E, Kroidl RF (1999) Wertigkeit der alveolokapillären Sauerstoffdifferenz (AaDO2) und des Sauerstoffpartialdruckverhaltens in der Spiroergometrie bei der Beurteilung von Gasaustauschstörungen. Atemw Lungenkrkh 4:220–226

Thompson WD, Walter SD (1988) A reappraisal of the kappa coefficient. J Clin Epidemiol 41:949–958

von Goethe JW (1819) West-oestlicher Divan, Talismane (The West-Eastern Divan, Talismane). Cotta'sche Buchhandlung, Stuttgart. Translation by E. Dowden: Toronto 1914. https://openlibrary.org/books/OL23359206M/ West-eastern_divan

Woitowitz HJ, Schacke G, Woitowitz RH (1969) Arterial blood gases in working men and women before and after graded work load. Int Arch Arbeitsmed 25:124–139