J. Alberto Neder, Mathieu Marillier, Anne-Catherine Bernard, Denis E. O'Donnell

alberto.neder@queensu.ca

Lung function corner

Transfer coefficient of the lung for carbon monoxide and the accessible alveolar volume: clinically useful if used wisely

Case history

A 67-year-old morbidly obese female (body mass index: 46.3 kg·m^{-2}) with a history of long-term cigarette smoking (>30 pack-years) was referred from Cardiology to Respirology due to progressive dyspnoea and recent findings of extensive mosaic attenuation of the lungs on a high-resolution computed tomography (HRCT) scan (figure 1). She had been followed by Cardiology on the grounds of multivalvular disease (severe aortic stenosis and moderate mitral regurgitation), ischaemic heart disease, hypertension and hypercholesterolaemia.

The patient reported exertional dyspnoea in the past 5 years, which had worsened markedly in the past year. In fact, her dyspnoea has progressed from a previous grade of 2 according to the 1–5 Medical Research Council scale to a current grade of 4. Apart from occasional, non-productive cough she denied any other respiratory symptom. As part of her pre-operative assessment for potential transcatheter aortic valve implantation, a chest radiograph showed ill-defined, bilateral haziness which was deemed inconsistent with her current haemodynamic status. As mentioned, a subsequent chest HRCT scan (figure 1) prompted referral to the respiratory service.

Question

How can the pulmonary function testing (PFT) laboratory be helpful in guiding further investigations to uncover the cause(s) of the abnormalities observed on chest HRCT?

Answer

The mosaic pattern of lung attenuation seen in figure 1 is characterised by a patchwork of regions of differing attenuation with well-defined borders
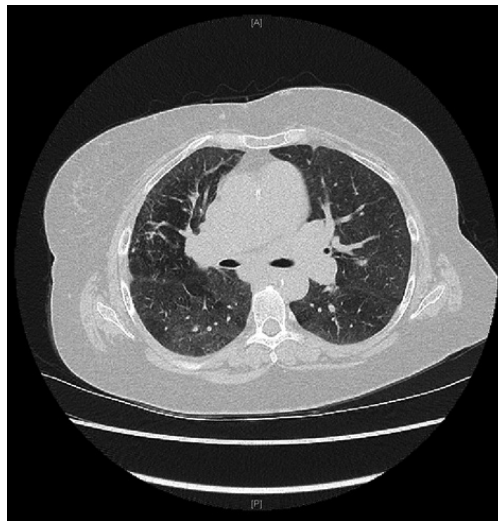

Figure 1 *A non-contrasted chest HRCT scan on inspiration showing diffuse areas of mosaic attenuation of the lungs with enlarged central pulmonary vessels and pulmonary artery trunk (3.6 cm).*

@ERSpublications
Transfer coefficient of the lung for carbon monoxide (KCO) and alveolar volume (VA) increase the yield of clinical information obtained from transfer factor of the lung for carbon monoxide (TLCO) measurements in clinical practice http://ow.ly/AVgu30na1vu

corresponding to the secondary pulmonary lobules [1]. As expected by the secondary lobules' anatomy, the mosaic pattern may be due to pulmonary vascular, small airway or infiltrative lung disease [2]. Infiltrative lung disease and airway disease can be reliably differentiated by an experienced radiologist. However, pulmonary vascular disease is often misinterpreted as an airway disease [1]. Comparing inspiratory and expiratory CT scans can be helpful in indicating the presence of gas trapping secondary to small airway disease although the support for this approach comes mainly from studies involving patients with high likelihood of gas trapping, *e.g.* asthma, bronchiolitis obliterans and cystic fibrosis [3–5]. Thus, clinical interpretation of PFTs in the current scenario should be focused on answering the following question: is the patient's mosaic pattern on chest HRCT more likely related to an airway- or a pulmonary vascular-centred disease?

Table 1 *Standard pulmonary function tests pre- and post-inhaled bronchodilator*

	Pre-bronchodilator	Post-bronchodilator
Spirometry		
FEV1 % pred	71	74
FVC % pred	75	74
FEV1/FVC	0.68	0.72
FEV1/SVC	0.64	0.65
FEF25-75% % pred	63	62
Body plethysmography		
TLC % pred	78	81
VC % pred	72	74
IC % pred	128[#]	121[#]
FRC % pred	69[#]	67[#]
ERV % pred	32[#]	29[#]
RV % pred	62[#]	68[#]
RV/TLC	0.47	0.46
Airway resistance		
R_{aw} % pred	122	138
sR_{aw} % pred	147	142
Gas exchange		
V_A % pred	72	76
V_A/TLC	0.89	0.90
T_{LCO} % pred	40[#]	38[#]
K_{CO} % pred	62[#]	58[#]

FEV1: forced expiratory volume in 1 s; FVC: forced expiratory volume; SVC: slow vital capacity; FEF25-75%: forced expiratory flow between 25 and 75% of FVC; TLC: total lung capacity; VC: vital capacity; IC: inspiratory capacity; FRC: functional residual capacity; ERV: expiratory reserve volume; RV: residual volume; R_{aw}: airway resistance; sR_{aw}: specific airway resistance; V_A: accessible alveolar volume; T_{LCO}: transfer factor of the lung for carbon monoxide; K_{CO}: transfer coefficient of the lung for carbon monoxide. [#]: abnormal test results (outside the 95% confidence interval).

Results of routine PFTs are shown in table 1. Spirometry was essentially within normal limits with a trend towards mild and proportional decrease in FEV1 and FVC either pre- or post-bronchodilator [6]. Body plethysmography also suggested a trend towards restriction with a borderline decrease in TLC, a high IC and a low ERV. There was no evidence of gas trapping either absolute (high RV) or relative (high RV/TLC); in fact, FRC and RV were low. The V_A, as determined by methane dilution in the single-breath T_{LCO} measurement [7], was normal-to-low in tandem with TLC, *i.e.* the V_A/TLC ratio was within normal limits (>0.8) [8–10]. Thus, there was no significant maldistribution of ventilation [9, 10] Of note, the haemoglobin-corrected T_{LCO} was severely reduced as well as the K_{CO} (T_{LCO}/V_A ratio) [11]. Inhaled bronchodilator had no significant effect on the recorded variables (table 1). Collectively, these results indicate: an incipient restrictive ventilatory defect coupled with other findings (increased IC, decreased FRC, decreased ERV and decreased RV) which could be largely ascribed to patient's body habitus (morbid obesity) [12]; associated with an out-of-proportion decrease in T_{LCO} and a severe impairment in gas exchange efficiency (low K_{CO}).

Thus, a pulmonary vascular aetiology was considered the most likely reason behind the observed mosaic pattern on the patient's HRCT.

Clinical follow-up

Based on the PFTs data suggesting pulmonary vascular disease and the mosaic pattern on HRCT with an enlarged pulmonary artery trunk, an urgent transthoracic echocardiogram confirmed pulmonary hypertension (PH). A ventilation/perfusion (V'/Q') scan was requested with a specific concern of thromboembolic disease [13]; in fact, it did show multiple segmental mismatched V'/Q' deficits. A CT pulmonary angiogram confirmed chronic thromboembolic material within dilated central pulmonary arteries. Right heart catheterisation results were consistent with pre-capillary PH (mean pulmonary arterial pressure: 39 mmHg, pulmonary arterial wedge pressure: 10 mmHg). In this context, the patient was diagnosed with chronic thromboembolic pulmonary hypertension (CTEPH) [13] and referred to the institutional PH clinic.

Discussion

The transfer of any inspired gas with the ability of binding to haemoglobin (*e.g.* O_2) in the red blood cells (RBCs) crossing the pulmonary capillaries depends on [14]:

- the pre-haemoglobin resistance to gas flow (literally from the mouth to the interior of the

RBCs), collectively called the "membrane" component; and

- the concentration and binding properties of haemoglobin.

When carbon monoxide (CO) is used instead of O_2 to assess the integrity of this complex process (haemoglobin's affinity for CO is 230 times that of O_2), it has been shown that ~80% of the T_{LCO} signal comes from the blood phase, *i.e.* the number of RBCs and/or the number of open capillary vessels (capillary volume, VC) [15]. It is therefore understandable that T_{LCO} is considered a "window to the pulmonary microcirculation" [16]. It may also partially explain why a low T_{LCO} is associated with increased areas of high ventilation–perfusion relationship [17]. It follows that patients with chronic obstructive pulmonary disease presenting with a low T_{LCO} need to ventilate in excess to a given metabolic load (*i.e.* poor exertional ventilatory efficiency) to overcome an enlarged physiological dead space [18]. Patients with low T_{LCO} (<50% predicted) are also at higher risk of presenting with another source of increased ventilatory stimuli: hypoxaemia [19]. Thus, a low T_{LCO} may be associated with a high respiratory neural drive on exertion, a key correlate of exertional dyspnoea [20]. It is not surprising, therefore, that a low T_{LCO} is an independent predictor of decreased physical activity in this patient population [21].

The clinical interpretation of T_{LCO}, however, might be confounded by the fact that it is critically dependent on:

1) the lung volume at which it is measured and, importantly,
2) "how many" gas exchanging unities at a given lung volume have received the inhaled gas mixture [22, 23].

Regarding the first point, T_{LCO} increases as the alveoli are distended because the surface area for gas exchange increases and because the alveolar–capillary membrane may become thinner. Conversely, as the lung deflates T_{LCO} decreases because the surface area decreases while it may become progressively thicker [24]. However, alveolar distension also compresses the lung capillaries, whereas alveolar emptying gives more space to capillary filling [25] (although this is partially compensated by a squeezing effect on the total intra-thoracic blood volume at very low lung volumes) [26]. It follows that [24–26]: from mid-lung volumes upwards, T_{LCO} increases less than it would be expected from the increase in V_A because the latter effect is partially counterbalanced by a (small) decrease in VC; and from mid-lung volumes downwards, T_{LCO} decreases less than it would be expected from the decrease in V_A because VC decreases less than the V_A [23]. The final result is a curvilinear, exponential-like increase in the VC/V_A ratio as the V_A diminishes. Translating those concepts to T_{LCO} measurements,
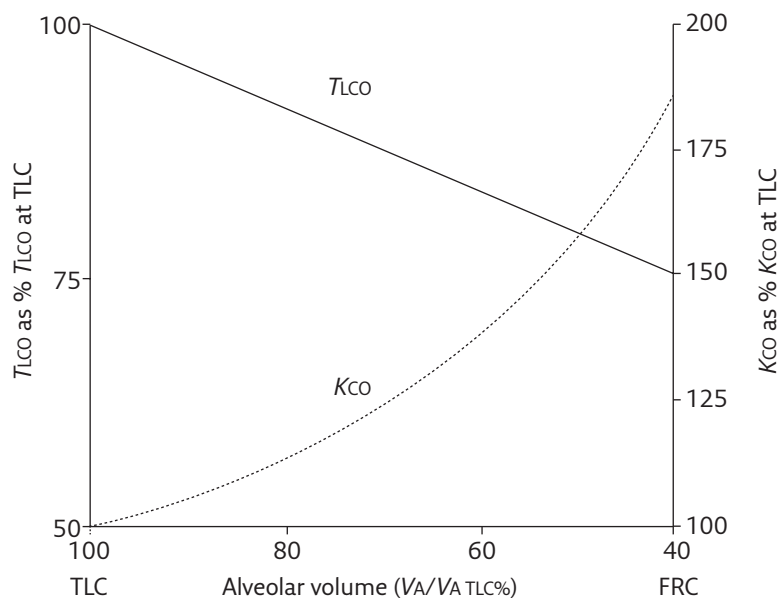

Figure 2 *The linear decrease in TLCO as the accessible VA decreases is associated with an exponential increase in KCO. For instance, TLCO decreases ~25% while KCO increases by ~90% from TLC to FRC. It follows that at a given VA below TLC, KCO (% predicted) will always be a higher value than TLCO (% predicted). See the text for further elaboration on the clinical interpretation of those measurements. VA/VA TLC%: accessible VA as a percentage of the VA found at TLC. Modified from [23] with permission from the publisher.*

they imply an essentially linear decrease in T_{LCO} but an exponential increase in K_{CO} (T_{LCO}/V_A) as V_A decreases (figure 2) [23]. These considerations carry important messages:

- they might lead to a "pseudo-normal" K_{CO} in a restrictive defect that decreases both T_{LCO} and V_A [27]; and
- 1 "unit" change in V_A does not lead to 1 "unit" change in T_{LCO} across all possible V_A values, *i.e.* it is highly misleading to state that "the T_{LCO}/V_A ratio represents T_{LCO} corrected by lung volume".

Concerning the second point, it should be remembered that during the T_{LCO} manoeuvre we measure only the fraction of TLC which can be accessed by the inhaled mixture (which is provided by V_A), a volume that depends on how well the peripheral units connect with the large airways [10, 28]. In most healthy subjects, the V_A/TLC ratio is ≥0.85 [8, 29] or ≥0.80 [9] provided that the subject performed a maximal inspiratory manoeuvre. However, in the presence of airway disease and extensive maldistribution of ventilation, V_A will be a poor representation of the lungs as a whole (TLC) and V_A/TLC ratio is <0.80–0.85 [28]. This might lead to a "pseudo-normal" K_{CO} in an obstructive defect that decreases V_A [27].

How to deal with these potential pitfalls in V_A and K_{CO} interpretation? We suggest the following simplified interpretation algorithm when T_{LCO} is reduced (figure 3) [23].

When V_A is normal there is a high negative predictive value for restriction (because V_A is always a fraction of TLC; thus, if V_A is normal so is TLC in
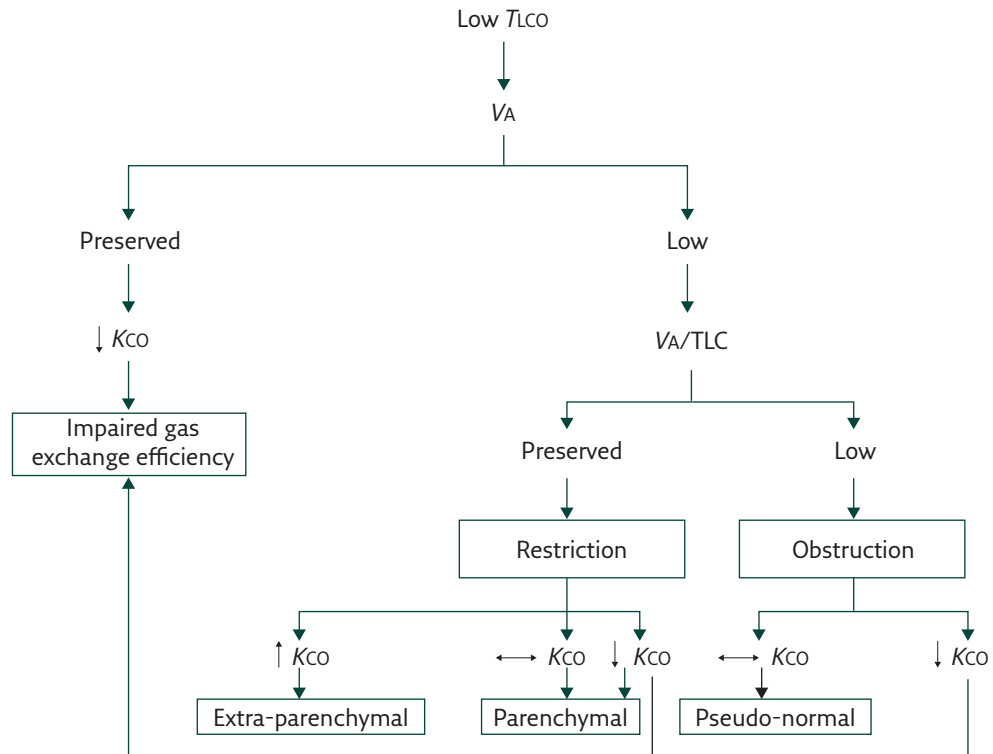
Figure 3 *A simplified algorithm for the differential diagnosis of a low TLCO taking into consideration the potential pitfalls involved in interpretation of the accessible VA and KCO. Symbols ↑, ↓ and ↔ represent values above, below and within the normal range, respectively. See the text for further elaboration.*

the great majority of subjects) [30]. If obstruction with maldistribution of ventilation were present, it would decrease V_A secondary to a low V_A/TLC [31]. It follows that a normal V_A, when associated with a low K_{CO} (provided there is no anaemia or recent smoking), suggests pulmonary vascular disease (*e.g.* PH or vasculitis), intrapulmonary right-to-left shunting or early emphysema, *i.e.* mild enough to not (yet) be associated with a low V_A/TLC.

When V_A is low the next step is to check the V_A/TLC ratio.

- If the V_A/TLC ratio is low (<0.8) indicating obstruction with ventilation distribution abnormalities [10, 28], the K_{CO} might turn "normal". In this scenario, no further valid inferences can be made regarding K_{CO}; however, if K_{CO} is low despite those caveats (which, as mentioned, would otherwise tend to increase the T_{LCO}/V_A ratio), there is extensive impairment in pulmonary gas exchange efficiency, *e.g.* severe emphysema [32].
- If the V_A/TLC ratio is normal (≥0.8), the only explanation for a low V_A is a low TLC, *i.e.* restriction [30]. Thus:
  1) A high K_{CO} indicates a predominance of VC over V_A due to: a) incomplete alveolar expansion but preserved gas exchange unities frequently leading to K_{CO} >120–140% or even higher, *i.e.* extra-parenchymal restriction (*e.g.* pleural, chest

wall or neuromuscular disease) [11]; b) an increase in pulmonary blood flow from areas of diffuse (pneumonectomy) or localised (local destructive lesions/atelectasis) loss of gas exchange units to areas with preserved parenchyma frequently leading to more modest increases in K_{CO} (although a high K_{CO} can also be seen with normal or near-normal V_A when there is increased pulmonary blood flow or redistribution such as left-to-right shunt and asthma); and c) extra-vascular haemoglobin, *i.e.* alveolar haemorrhage.

2) A low K_{CO} points towards intra-parenchymal restriction with impaired gas exchange efficiency as in some interstitial lung diseases (ILD) [33].
3) A normal K_{CO} is consistent with intra-parenchymal restriction with preserved K_{CO}. This is the most common finding in patients with HRCT abnormalities showing a pattern consistent with idiopathic interstitial pneumonia [33]. Thus, a normal K_{CO} should not be misinterpreted as indicative of "no ILD" [34, 35]. In this context, a normal K_{CO} may either indicate that the main mechanism underlying the low T_{LCO} is loss of lung volume (*e.g.* fibrotic ILD) or the low V_A led to a normalisation of K_{CO} due to the curvilinear increase in K_{CO} as V_A decreases (figure 2).

Table 2 *Key recommendations to avoid frequent pitfalls in the interpretation of T*LCO, *K*CO *and V*A *in clinical practice*

Recommendation	Justification
Always rule out anaemia and recent smoking (*i.e.* CO inhalation) as a cause for a low *T*LCO.	Decreases the number of haemoglobin sites available for CO binding and higher CO back-pressure, respectively.
The *T*LCO/*V*A ratio does not represent "*T*LCO corrected by lung volume". To avoid confusion and misinterpretation, *K*CO should always be used instead of *T*LCO/*V*A.	A one unit change in *V*A does not necessarily lead to one unit change in *T*LCO.
A "preserved" *K*CO should never be interpreted as indication of no major pulmonary pathology.	In both obstructive and restrictive diseases *V*A may decrease out-of-proportion to *T*LCO leading to a "pseudo-normal" *K*CO.
The first step in the interpretation of *K*CO in the presence of a low *V*A is to check the *V*A/TLC ratio.	If low (<0.8) there is maldistribution of ventilation, frequently leading to a "pseudo-normal" *K*CO.
Rule out submaximal inspiration (inspired volume should be at least 85% of the largest VC) as the cause of a low *V*A before interpreting a high *K*CO.	Due to the marked increase in *K*CO as *V*A decreases, relatively small decrements in the latter has a major impact on *K*CO.
Always grade the functional impairment based on decrease in *T*LCO not in *K*CO.	

Owing to the trend for *K*CO to be higher than *T*LCO regardless the underlying reason(s), the severity of functional impairment should always be gradated based on *T*LCO based on the European Respiratory Society recommendations: mild (less than lower limit of normal, but above 60% predicted according to the recently published Global Lung Initiative equations [36]), moderate (40–60% predicted) and severe (>40% predicted) [6].

In the present case, a low *V*A but normal *V*A/TLC (coupled with the absence of obstruction on spirometry, gas trapping or high specific airway resistance) is not consistent with maldistribution of ventilation due to small airway disease. Thus, *V*A decreased in proportion to a low TLC, *i.e.* secondary to the patient's morbid obesity and/or to the known trend for CTEPH patients to present with mild restriction due to microatelectasis and fibrotic changes [37]. As shown in figure 2, *K*CO should increase as *V*A decreases if there was no impairment in gas exchange efficiency; in fact, this is one of the justifications as to why obesity is associated with a high *K*CO [38]. It follows that the only plausible explanation for a low *K*CO in the present case is a low VC, *i.e.* a pulmonary vascular disease. Some key interpretative issues regarding *T*LCO and its derived measurements are provided in table 2.

Key points

- Clinical interpretation of the *T*LCO frequently benefits from associated analysis of the accessible *V*A, *V*A/TLC ratio and the diffusion coefficient (*K*CO).
- The *T*LCO/*V*A ratio (*K*CO) should not be erroneously interpreted as "*T*LCO corrected by lung volume" because a one unit change in *V*A does not lead to one unit change in *T*LCO across all possible *V*A values.
- Preserved *V*A and a low *K*CO (provided the absence of anaemia or recent smoking) suggests pulmonary vascular disease, intrapulmonary right-to-left shunting or early emphysema.
- A low *V*A in the presence of a normal *V*A/TLC ratio suggests restriction: a low *K*CO points towards intra-parenchymal restriction with impaired gas exchange efficiency whereas a high *K*CO is consistent with extra-parenchymal restriction.
- A low *V*A in the presence of a low *V*A/TLC ratio indicates obstruction with ventilation distribution abnormalities: whereas a preserved *K*CO is not amenable to interpretation, a low *K*CO indicates extensive impairment in pulmonary gas exchange efficiency, *e.g.* severe emphysema.
- A normal *K*CO should not be used to rule out major pulmonary pathology, particularly when *V*A is reduced.

Self-evaluation questions

In each of the following patients, please indicate which is the most likely underlying diagnosis which could explain the observed abnormalities (indicated by a # symbol).

1.

TLC % pred	T_{LCO} % pred	V_A % pred	V_A/TLC	K_{CO} % pred
132#	52#	64#	0.56#	87

a) Idiopathic PH
b) Neuromuscular disease
c) Emphysema
d) Asthma
e) ILD

2.

TLC % pred	T_{LCO} % pred	V_A % pred	V_A/TLC	K_{CO} % pred
50#	68#	44#	0.97	145#

a) Idiopathic PH
b) Neuromuscular disease
c) Emphysema
d) Asthma
e) ILD

3.

TLC % pred	T_{LCO} % pred	V_A % pred	V_A/TLC	K_{CO} % pred
91	54#	82	0.86	64#

a) Idiopathic PH
b) Neuromuscular disease
c) Emphysema
d) Asthma
e) ILD

4.

TLC % pred	T_{LCO} % pred	V_A % pred	V_A/TLC	K_{CO} % pred
69#	44#	67#	0.93	58#

a) Idiopathic PH
b) Neuromuscular disease
c) Emphysema
d) Asthma
e) ILD

5.

TLC % pred	T_{LCO} % pred	V_A % pred	V_A/TLC	K_{CO} % pred
107	112	99	0.82	129#

a) Idiopathic PH
b) Neuromuscular disease
c) Emphysema
d) Asthma
e) ILD

Affiliations

J. Alberto Neder, Mathieu Marillier, Anne-Catherine Bernard and Denis E O'Donnell

Laboratory of Clinical Exercise Physiology and Respiratory Investigation Unit, Division of Respirology and Sleep Medicine, Dept of Medicine, Kingston Health Science Center and Queen's University, Kingston, ON, Canada.

Conflict of interest

None declared.

References

1. Kligerman SJ, Henry T, Lin CT, *et al*. Mosaic attenuation: etiology, methods of differentiation, and pitfalls. *Radiographics* 2015; 35: 1360–1380.
2. Stern EJ, Müller NL, Swensen SJ, *et al*. CT mosaic pattern of lung attenuation: etiologies and terminology. *J Thorac Imaging* 1995; 10: 294–297.
3. Collins J. CT signs and patterns of lung disease. *Radiol Clin North Am* 2001; 39: 1115–1135.
4. Jensen SP, Lynch DA, Brown KK, *et al*. High-resolution CT features of severe asthma and bronchiolitis obliterans. *Clin Radiol* 2002; 57: 1078–1085.
5. Dorlöchter L, Nes H, Fluge G, *et al*. High resolution CT in cystic fibrosis--the contribution of expiratory scans. *Eur J Radiol* 2003; 47: 193–198.
6. Pellegrino R, Viegi G, Brusasco V, *et al*. Interpretative strategies for lung function tests. *Eur Respir J* 2005; 26: 948–968.
7. Graham BL, Brusasco V, Burgos F, *et al*. ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J* 2017; 49: 1600016.
8. Cotes JE. Assessment of distribution of ventilation and of blood flow through the lung. Lung Function. Assessment and Application in Medicine. Oxford, Blackwell Scientific Publications, 1993; pp. 213–262.
9. Neder JA, O'Donnell CDJ, Cory J, *et al*. ventilation distribution heterogeneity at rest as a marker of exercise impairment in mild-to-advanced COPD. *COPD* 2015; 12: 249–256.
10. Davis C, Sheikh K, Pike D, *et al*. Ventilation heterogeneity in never-smokers and COPD: comparison of pulmonary functional magnetic resonance imaging with the poorly communicating fraction derived from plethysmography. *Acad Radiol* 2016; 23: 398–405.
11. Hughes JM, Pride NB. In defence of the carbon monoxide transfer coefficient Kco (TL/VA). *Eur Respir J* 2001; 17: 168–174.
12. Bernhardt V, Babb TG. Exertional dyspnoea in obesity. *Eur Respir Rev* 2016; 25: 487–495.
13. Gopalan D, Blanchard D, Auger WR. Diagnostic evaluation of chronic thromboembolic pulmonary hypertension. *Ann Am Thorac Soc* 2016; 13: Suppl. 3, S222–S239.
14. Hughes JMB, Bates DV. Historical review: the carbon monoxide diffusing capacity (DLCO) and its membrane (DM) and red cell (θ.Vc) components. *Respir Physiol Neurobiol* 2003; 138: 115–142.
15. Hughes JMB, Dinh-Xuan AT. The DLNO/DLCO ratio: physiological significance and clinical implications. *Respir Physiol Neurobiol* 2017; 241: 17–22.
16. Hughes JMB. The single breath transfer factor (Tlco) and the transfer coefficient (Kco): a window onto the pulmonary microcirculation. *Clin Physiol Funct Imaging* 2003; 23: 63–71.
17. Robertson HT. Dead space: the physiology of wasted ventilation. *Eur Respir J* 2015; 45: 1704–1716.
18. Neder JA, Berton DC, de Müller PT, *et al*. Ventilatory inefficiency and exertional dyspnea in early chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2017; 14: Suppl. 1, S22–S29.
19. Andrianopoulos V, Franssen FME, Peeters JPI, *et al*. Exercise-induced oxygen desaturation in COPD patients without resting hypoxemia. *Respir Physiol Neurobiol* 2014; 190: 40–46.
20. Mahler DA, O'Donnell DE. Recent advances in dyspnea. *Chest* 2015; 147: 232–241.
21. Garcia-Aymerich J, Serra I, Gómez FP, *et al*. Physical activity and clinical and functional status in COPD. *Chest* 2009; 136: 62–70.
22. Comroe JH. Pulmonary diffusing capacity for carbon monoxide (DLCO). *Am Rev Respir Dis* 1975; 111: 225–228.
23. Hughes JMB, Pride NB. Examination of the carbon monoxide diffusing capacity (DL(CO)) in relation to its KCO and VA components. *Am J Respir Crit Care Med* 2012; 186: 132–139.
24. Stam H, Versprille A, Bogaard JM. The components of the carbon monoxide diffusing capacity in man dependent on alveolar volume. *Bull Eur Physiopathol Respir* 1983; 19: 17–22.
25. Stam H, Kreuzer FJ, Versprille A. Effect of lung volume and positional changes on pulmonary diffusing capacity and its components. *J Appl Physiol* 1991; 71: 1477–1488.
26. Frans A, Nemery B, Veriter C, *et al*. Effect of alveolar volume on the interpretation of single breath DLCO. *Respir Med* 1997; 91: 263–273.
27. Cotes JE. Carbon monoxide transfer coefficient KCO (TL/VA): a flawed index. *Eur Respir J* 2001; 18: 893–894.
28. Ross JC, Ley GD, Krumholz RA, *et al*. A technique for evaluation of gas mixing in the lung: studies in cigarette smokers and nonsmokers. *Am Rev Respir Dis* 1967; 95: 447–453.
29. Roberts CM, MacRae KD, Seed WA. Multi-breath and single breath helium dilution lung volumes as a test of airway obstruction. *Eur Respir J* 1990; 3: 515–520.
30. Odo NU, Mandel JH, Perlman DM, *et al*. Estimates of restrictive ventilatory defect in the mining industry. Considerations for epidemiological investigations: a cross-sectional study. *BMJ Open* 2013; 3: e002561.
31. Punjabi NM, Shade D, Wise RA. Correction of single-breath helium lung volumes in patients with airflow obstruction. *Chest* 1998; 114: 907–918.
32. Kahnert K, Jobst B, Biertz F, *et al*. Relationship of spirometric, body plethysmographic, and diffusing capacity parameters to emphysema scores derived from CT scans. *Chron Respir Dis* 2018; 16: 1479972318775423.

Suggested answers

1. c. Moderately reduced T_{LCO}. Low V_A is associated with a low V_A/TLC and a high TLC indicating extensive ventilation distribution abnormalities in the context of an obstructive airway disease. Of note, despite low V_A/TLC, K_{CO} is reduced indicating extensive impairment in gas exchange efficiency. Collectively, emphysema is the most likely explanation for these findings.

2. b. Mildly reduced T_{LCO}. Markedly low V_A is associated with an equally low TLC and preserved V_A/TLC. Thus, K_{CO} is supra-normal. Collectively, these results are in line with extra-parenchymal restriction. Given the options available, neuromuscular disease is the most likely explanation for these findings (differentials being pleural and chest wall disease).

3. a. Moderately reduced T_{LCO}. V_A, TLC and V_A/TLC are within normal limits. Thus, K_{CO} is reduced. Collectively, the results are in line with impaired intrapulmonary gas exchange efficiency in the absence of restriction or significant airway disease. Given the options available, idiopathic PH is the most likely explanation for these findings (differentials being other pulmonary vascular diseases and right-to-left shunt).

4. e. Moderate-to-severe impairment in T_{LCO}. Low V_A is associated with an equally low TLC and preserved V_A/TLC. K_{CO} is also reduced. Collectively, the results are in line with intra-parenchymal restriction. Given the options available, ILD (with impaired gas exchange efficiency) is the most likely explanation for these findings.

5. d. Preserved T_{LCO} but supra-normal K_{CO} in the context of normal TLC. Given the options available, asthma is the most likely explanation for these findings (differential being left-to-right shunt).

33. Wallaert B, Wemeau-Stervinou L, Salleron J, et al. Do we need exercise tests to detect gas exchange impairment in fibrotic idiopathic interstitial pneumonias? *Pulm Med* 2012; 2012: 657180.

34. Enright MP. Office-based DLCO tests help pulmonologists to make important clinical decisions. *Respir Investig* 2016; 54: 305–311.

35. van der Lee I, Zanen P, van den Bosch JMM, et al. Pattern of diffusion disturbance related to clinical diagnosis: The K(CO) has no diagnostic value next to the DL(CO). *Respir Med* 2006; 100: 101–109.

36. Cooper BG, Stocks J, Hall GL, et al. The Global Lung Function Initiative (GLI) Network: bringing the world's respiratory reference values together. *Breathe (Sheff)* 2017; 13: e56–e64.

37. Jenkins D, Mayer E, Screaton N, et al. State-of-the-art chronic thromboembolic pulmonary hypertension diagnosis and management. *Eur Respir Rev* 2012; 21: 32–39.

38. Collard P, Wilputte JY, Aubert G, et al. The single-breath diffusing capacity for carbon monoxide in obstructive sleep apnea and obesity. *Chest* 1996; 110: 1189–1193.