Interpretation of increases in the transfer coefficient for carbon monoxide (TLCO/VA or KCO)

D J LIPSCOMB,¹ KANTA PATEL, AND J M B HUGHES

From the Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0HS, UK

Lipscomb, D J, Patel, K, and Hughes, J M B (1978). *Thorax*, 33, 728–733. **Interpretation of increases in the transfer coefficient for carbon monoxide (TLCO/VA or KCO).** During a 15-month period, 27 patients were seen in a routine clinical pulmonary function laboratory in whom the transfer coefficient (TLCO/VA or KCO), measured by the single breath technique, was increased. Pulmonary haemorrhage accounted for two-thirds of the cases; in them sequential measurements of KCO were able to monitor the onset and cessation of bleeding. In the remaining cases the cause of the increase in KCO remains uncertain. All patients had a reduction in vital capacity. Experiments in six normal subjects showed that KCO rose as the breath-holding lung volume was reduced, but that this was insufficient to account for the raised KCO in patients with reduced volumes. Partitioning of the two components of TLCO at different lung volumes in three normal subjects showed that an increase in pulmonary capillary blood volume per unit alveolar volume was chiefly responsible for the increase of KCO in normal subjects at lower lung volumes. The membrane diffusing capacity changed less than predicted per unit volume, suggesting that the thickness of the air-blood barrier remains fairly constant as the lung expands or contracts.

Modern interpretation of the carbon monoxide diffusing capacity stems from the work of Roughton (1945) and Roughton and Forster (1957), who proposed that the conductance of CO (DLCO) from alveolar gas to pulmonary capillary blood was inversely proportional to the sum of two resistances—that afforded by the tissue interposed between alveolar gas and the red cells in the capillary and that related to the chemical combination of CO with haemoglobin, that is,

$$1/DL = 1/Dm + 1/\theta Vc \dots \dots (1)$$

where DL is the total conductance for CO, Dm the tissue or membrane conductance, θ the rate of combination of CO with haemoglobin, and Vc the pulmonary capillary blood volume that is proportional to the number of haemoglobin combining sites. Thus it is more correct to refer to the transfer of CO (TLCO) from alveolar gas to blood than to diffusion (DLCO) since the latter contributes only part of the process.

With the introduction of a standardised single breath test for measuring CO transfer (Ogilvie *et al*, 1957) and its widespread clinical application,

increasing attention has been paid to the lung volume in which the CO is distributed. The transfer factor per unit alveolar volume (TLCO or KCO), where VA represents the volume of distribution of CO during the breath-holding manoeuvre, reflects the performance of the ventilated parts of the lung independent of their size. A low TLCO may occur in emphysema because of acinar lung damage or in asthma because of maldistribution of inspired gas, but the KCO will be low in the former instance and normal in the latter. Thus the KCO can be valuable in interpreting abnormalities of TLCO.

In the past, interest has focused on conditions such as emphysema and lung fibrosis where TLCO and KCO have been reduced. Nevertheless, it was recently shown in this laboratory that a high KCO was associated with the lung haemorrhage that occurred in Goodpasture's syndrome (Ewan *et al*, 1976). The presence of a stagnant, presumably extravascular, pool of blood in these patients was shown by a low rate of clearance of inhaled radioactive carbon monoxide (C¹⁵O) from the lung, as monitored by external counting, at a time when the removal of CO from alveolar gas

¹Present address: Peterborough District Hospital, Peterborough, Cambs.

was high. Serial measurements showed that the Kco returned rapidly to normal when haemorrhage was judged, on clinical and radiological grounds, to have stopped.

Over a 15-month period we noted all cases that were associated with a high Kco. Although most were caused by lung haemorrhage from various causes, nearly one-third were associated with conditions in which a raised TLCO or Kco had not been described. In addition, we measured Kco, Dm, and Vc in normal subjects at different lung volumes to see whether lung volume restriction caused the raised Kco in some patients without lung haemorrhage.

Subjects and methods

The routine assessment of pulmonary function in our laboratory includes measurements of forced expiratory volume in one second (FEV₁), vital capacity, lung volumes by body plethysmography, and transfer factor for carbon monoxide (TLCO) and Kco by the single breath method (Ogilvie *et al.*, 1957). TLCO and Kco are corrected for the concentration of haemoglobin (Cotes *et al.*, 1972). The results are considered potentially abnormal if they lie outside one standard deviation of our predicted normal values, that is, those recommended by Cotes (1975). For the purpose of this study, a raised Kco was diagnosed only if it exceeded the predicted value for Kco (van Ganse *et al.*, 1972) by two standard deviations. All cases seen in a 15-month period (1976–7) were included.

In six normal non-smoking subjects Kco was measured at different degrees of lung expansion. Subjects inhaled from residual volume in the usual way, and a solenoid-operated shutter, triggered by the potentiometer on the spirometer, closed off the inspired line at a preset volume. In any subject the measurements were spread over several days, a maximum of four measurements being made on any single day. At this level of exposure, measurements of CO back pressure were not required. In a further three normal subjects (non-smokers) Dm and Vc were measured using the standard concentration of carbon monoxide at different inspired oxygen tensions. On successive days the subjects breathed in open circuit 21, 39, 59, or 88% oxygen in nitrogen for 15 minutes. Measurements of single breath TLCO and Kco at functional residual capacity (FRC) and total lung capacity (TLC) were made in the order TLC, FRC, TLC, FRC using a carbon monoxide (0.3%)–helium (10%) mixture with the same oxygen concentration. At FRC and TLC, the first 0.75–1.0 l of the expirate was discarded before the alveolar sample

was taken. After each single breath the subject was switched back to the open circuit gas mixture until all four measurements were complete. The inspired and expired bag gases were analysed for their oxygen, carbon monoxide, and helium concentrations. The helium catharometer was calibrated for the different oxygen concentrations. Before the last measurement, the subject was turned into a closed circuit system, with a CO₂ absorber, and rebreathed the same oxygen-nitrogen mixture from a six-litre bag for three minutes. The bag was later analysed for its CO concentration, and the plasma back pressure of carbon monoxide was calculated. The value was always very low (<0.007%) and had little effect on the calculations. The calculation of θ , Dm, and Vc was made as described by Cotes (1975). In the calculation of θ (see Cotes, 1975, p 258), the coefficients α and β (intercept and slope of $1/\theta$ against PO₂ derived experimentally on blood in vitro (Holland, 1969)) were taken as 1×10^{-3} kPa l min⁻¹ min and 0.134×10^{-3} l mmol⁻¹ min respectively. The value for α assumes that λ (ratio of the resistance of the red cell membrane to that of the interior is infinite. The saturation of haemoglobin with CO was assumed to be negligible, and a haemoglobin concentration of 14.6 g/dl was assumed (actual values were 14.3, 14.6, and 15 g/dl). The plasma oxygen tension in the pulmonary capillary blood was calculated from the expired alveolar sample from each measurement, after analysis for CO and helium, as described by Cotes (1975, p 259), assuming an oxygen uptake of 12 mmol min⁻¹.

Results

Table 1 lists the diagnoses associated with a raised Kco. Lung haemorrhage was diagnosed on the basis of C¹⁵O measurements (Ewan *et al.*, 1976), a rise and fall in Kco, and a fall in haemoglobin concentration or haemoptysis, though the latter was often slight. The individual results are shown in fig 1 for those with Goodpasture's syndrome, those with other causes of lung bleeding, and those without lung haemorrhage.

Serial measurements were made in the cases associated with lung haemorrhage, and table 1 and fig 1 record the highest values achieved. In several cases, especially in Goodpasture's syndrome, more than one episode of bleeding was reported. This is illustrated, for a case of presumed idiopathic pulmonary haemosiderosis, in fig 2. The patient was a 13-year-old Asian girl with a two-year history of seropositive rheumatoid disease. The chest radiograph showed bilateral infiltration

Table 1 List of causes of raised Kco (TLco/VA) with values of Kco and vital capacity (VC) as percentage of predicted values

	No	Kco % pred	Vc % pred
Lung haemorrhage			
Goodpasture's syndrome	9	184	71
Immune complex rapidly progressively nephritis	1	158	80
Polyarteritis nodosa	3	174	81
Penicillamine sensitivity with rheumatoid arthritis	1	155	67
Pulmonary haemosiderosis	1	196	60
Leukaemia and thrombocytopenia	1	140	40
Inhalation of blood (bronchial haemorrhage)	1	251	76
Carcinoma of thyroid	1	148	67
Without lung haemorrhage			
Pleural mesothelioma	1	204	50
Pneumothorax	1	149	59
Myotonia congenita	1	158	68
Bilateral diaphragm paralysis	1	140	72
Obesity	2	158	62
Pneumonectomy	1	140	66
Polycythemia rubra vera	2	151	68

Fig 1 Kco (TLc/VA) as percentage predicted level associated with Goodpasture's syndrome, other causes of lung haemorrhage (see table 1), and cases without haemorrhage. Horizontal bars indicate mean values for the group.

of the peripheral lung fields. Pulmonary function test results showed some reduction in TLC and vital capacity. A lung biopsy showed thickened basement membrane and haemosiderin-laden alveolar macrophages. Treatment with prednisolone was started, but in mid-December, while taking steroids, she developed profound breathlessness accompanied by a considerable increase in the shadowing on the chest radiograph. Opportunistic infection was considered but the large increase in

Fig 2 Serial measurements of Kco in case of idiopathic haemosiderosis (see text for details). Shaded area indicates predicted range of Kco (mean $\pm$ 1 SD).

Kco was typical of pulmonary haemorrhage (fig 2); pulmonary bleeding occurred on two further occasions. Haemoptysis was negligible, but there were appreciable falls in haemoglobin concentration with each episode. Intensive treatment with plasma exchange and immunosuppressive drugs produced a clinical remission.

The change of Kco at different degrees of lung expansion is shown in fig 3 for six normal subjects. Kco increases exponentially as lung volume is reduced. In fig 4 the data from normal subjects are compared with the high Kco values found in patients without lung haemorrhage. Quite clearly a reduction in lung volume cannot be invoked to explain their high Kco.

Fig 3 Kco as a percentage of Kco at maximum inflation (TLC) in six normal subjects plotted against inspired volume (from residual volume) before breath-holding as a percentage of their vital capacity.

Fig 4 Kco as percentage predicted level for patients without lung haemorrhage against inspired volume as percentage predicted vital capacity (see last column fig 1). Range found in normal subjects (see fig 3) is shaded.

Calculations of Dm and Vc at two lung volumes in three normal subjects are shown in table 2. They were calculated from a graphical plot of 1/DL against 1/ θ (Cotes, 1975) where the intercept on the ordinate represents 1/Dm and the slope of the line 1/Vc (fig 5). For all subjects the points fitted a straight line as closely as in fig 5, except for the measurement of TLCO on 88% oxygen in case 3. The slopes and intercepts were calculated by linear regression, the correlation coefficients were >0.995, except in the case already mentioned where it was 0.987.

Discussion

The patients in this study were highly selected. Except for Goodpasture's syndrome, the frequency with which a high Kco is found in association with the other diagnoses listed in table 1 is not known, but its occurrence is probably uncommon. Nevertheless, the recognition (or suspicion) of lung

Fig 5 Case 2. Measurements of reciprocal of TLCO in a normal subject at FRC and TLC against 1/ θ representing four different alveolar oxygen tensions. Each point is mean of two measurements. Slope of line equals 1/Vc and intercept 1/Dm.

haemorrhage from a high Kco value in, say, leukaemia with thrombocytopenia, may be important. In the interpretation of chest radiographic shadowing in immunocompromised patients it is usually difficult to decide between infection, oedema, and haemorrhage. Haemosiderin-laden macrophages have been obtained by bronchial lavage in such patients (Drew *et al*, 1977), and they may bleed more often than is generally supposed.

Serial measurements of Kco might be particularly useful in diagnosing and monitoring those cases labelled as idiopathic pulmonary haemosiderosis (IPH). Kallenbach *et al* (1977) have stressed the association of IPH with various connective tissue and allergic disorders, such as rheumatoid arthritis, systemic sclerosis, systemic lupus erythematus, immune complex nephritis, polyarteritis, and Wegener's granulomatosis. Vascular damage to the lung, in the form of haemorrhage, might be recognised more often if unexplained falls in haemoglobin concentrations or shadows on the chest radiograph were accompanied by measurements of pulmonary diffusing capacity. It must be emphasised that pulmonary

Table 2 Anthropometric data in three normal subjects and partitioning of Kco into membrane conductance (Dm) and pulmonary capillary blood volume (Vc) at different alveolar volumes

Case No	Height (cm)	Weight (kg)	Age (years)	VA (litres BTPS)	Kco (mmol min ⁻¹ kPa ⁻¹ l ⁻¹)	Dm (mmol min ⁻¹ kPa ⁻¹)	Vc (ml)
1	176	74	32	6.4	1.7	28.7	127
				3.4	2.4	20.4	103
2	185	95	30	6.9	1.5	58.8	92
				3.3	2.2	21.0	87
3	193	91	30	8.0	1.5	45.0	106
				3.9	2.4	22.4	116

capillary haemorrhage is intermittent and that carbon monoxide only combines with freshly shed blood. Therefore a normal Kco cannot exclude the possibility that haemorrhage had occurred 48 hours earlier (fig 2).

The cause for the high Kco in the patients without lung haemorrhage is unclear. The reduction in lung volume in patients with muscle weakness or obesity did not appear to explain it (fig 4). Occult lung haemorrhage is possible in pleural mesothelioma. In pneumothorax and pneumonectomy diversion of blood flow and volume to the remaining or the ventilated lung might increase the transfer factor per unit volume. The increase in Kco, after correction for the high haemoglobin concentration, in polycythaemia rubra vera is interesting. It has not been noted previously (Burgess and Bishop, 1963). Possibly the lung may share in the general expansion of the vascular compartment that often occurs (Herbert *et al*, 1965). The haemoglobin-corrected Kco in one of our cases fell into the normal range after correction of his polycythaemia with ^{32}P and venesections.

The increase in Kco, as lung volume is reduced in normal subjects, is similar to that reported by McGrath and Thomson (1959). It was insufficient to explain the increase of Kco found in patients with small lung volumes (fig 4). TLCO in the normal subjects decreased as the inspired volume was reduced at a rate of about 3.3% per 10% decrease of vital capacity; this is similar to values quoted elsewhere (Cotes and Hall, 1970).

The factors that lead to an increase in Kco at low lung volumes may be seen in table 2, where TLCO has been partitioned into the conductance of CO through the alveolar-capillary membranes (Dm) and conductance with the red cell, that is, combination with haemoglobin (Vc). Our results are set out alongside previous reported data in table 3. Considering the technical difficulties of the measurements, the results from the different

studies are extremely consistent. Dm increases as lung volume rises. The Dm/VA ratios are constant at different volumes (less than 12% difference) except in the study of Miller and Johnson (1966) where there was a 24% difference, which suggests that Dm changes in direct proportion to volume. Gurtner and Fowler (1971) studied their subjects in the supine position with a rebreathing method; this removes most of the effect of uneven ventilation to volume (V/VA) and diffusion to volume (TL/VA) ratios. The other studies used the sitting position and the single breath method.

Morphological evidence also suggests that surface area changes in direct proportion to gas volume (Gil and Weibel, 1972), and that, above FRC, the alveoli maintain a constant shape (Klingele and Staub, 1970). If the lung expands as a sphere (or any similar shape), or by the recruitment of spheres, its surface area will change by $VA^{2/3}$ and its membrane thickness, assuming a constant tissue volume, will decrease. Since diffusion is proportional to area/thickness, Dm should in theory increase in proportion to $VA^{4/3}$. On morphological grounds, there appear to be adequate changes of alveolar surface per unit lung volume, but the harmonic mean barrier thickness changes little (Gil and Weibel, 1972), and this may account for the modest changes in Dm as a function of VA. Weibel's (1973) explanation for this is an attractive one. Electron micrographs show that the parts of the alveolar septum directly separating alveolar gas from capillary blood are the thinnest portions. The vast majority of the thicker barrier elements, such as cell bodies of endothelial and epithelial cells, type II cells, and connective tissue fibres are displaced toward the centre of the septum; thus a thin membrane of constant thickness is maintained between gas and blood at all lung volumes.

Pulmonary capillary blood volume (Vc) remains essentially the same at all lung volumes; thus the ratio Vc/VA doubles as lung volume is reduced

Table 3 Partitioning of membrane resistance (Dm) and pulmonary capillary blood volume (Vc) at different alveolar volumes (VA)

Author	No of subjects	VA l BTFS	Dm* (ml min ⁻¹ mmHg ⁻¹)	Dm/VA	Vc (ml)	Vc/VA	Dm/Vc
Hamer (1963)	7	7.02	62	8.8	87	12.4	0.71
		4.0	35	8.77	89	22.3	0.39
Miller and Johnson (1966)	5	6.7	77	11.5	90	13.4	0.87
		3.4	51	15.0	102	30.0	0.49
Gurtner and Fowler (1971)	3	5.5	89	16.2	82	14.9	0.9
		4.4	63	14.3	91	20.7	0.69
This study	3	7.1	144	18.6	108	15.2	1.22
		3.5	64	18.25	102	28.9	0.62

*SI units not used to enable direct comparison with Vc to be made.

from TLC to FRC. This is the principal cause of the rise in TLco/VA (Kco) at lower lung volumes. Using morphometric techniques in isolated lungs, Glazier *et al* (1969) showed that the volume of blood per unit septal length decreased by about 30% as the lung was expanded from 10 to 25 cm H₂O transpulmonary pressure, keeping a constant relationship between pulmonary arterial and alveolar pressures. On the other hand, septal length will increase (in proportion to VA^{1/3}) by 20%, the corner vessels in the alveoli will enlarge as perivascular pressure falls, and mean capillary pressure may rise. Presumably, these opposing effects balance each other.

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Requests for reprints to: Dr J M B Hughes, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0HS.