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2—Clinical considerations

The single-breath test for measuring carbon monoxide transfer is swift and painless for both patient and operator and, considering the great number of variables involved, it is surprisingly reproducible. The snags are the relatively high cost and complexity of the equipment, the need for the patient to be well enough to co-operate in breathing manoeuvres, and the intellectual discomfort of not knowing exactly what is being measured. Notwithstanding this last objection, the test does seem to have some empirical value and now—after 25 years' experience—its role in clinical practice can be more clearly defined.

Abnormalities of carbon monoxide transfer may be due to faults in matching at the air-blood interface, in the diffusing membrane itself, or in the pulmonary capillary blood. The same disease process can of course give rise to more than one of these three faults, sometimes with opposing effects. For example, in chronic obstructive lung disease, carbon monoxide transfer might be increased by recruitment of alveoli or capillaries enlarging the area of membrane available for diffusion, or by polycythaemia; on the other hand, it may be reduced by mismatching of air and blood or by destruction of alveoli and capillaries by emphysema. When separate measurements of membrane diffusion (DM) and pulmonary capillary volume (Vc) are not available, the clinician must attempt to interpret the overall result of the carbon monoxide transfer test according to whether it is normal, low, high, or (in serial measurements) changing from one to the other (see table, p8). In every case it is important to take into account the lung volume at which the measurement was made and, if this is itself abnormally high or low, to calculate the carbon monoxide transfer per unit of lung volume (diffusion coefficient: KCO).

There are many formulae for the prediction of normal values, most of them based on age, sex, and height. The formula most widely used is that of Cotes.[1] There is, however, some disagreement between these formulae[2] and factors other than age, sex, and height may determine the value obtained. Apart from differences between laboratories in the performance and analysis of the breath-holding manoeuvre[3] and in the measurement of lung volume,[4] there are physiological and environmental variables such as posture,[5] weather,[6] diurnal fluctuations,[7] altitude,[8] levels of habitual activity,[9] and hormonal influences.[10 11] Ideally, each clinical laboratory should standardise its own technique, establish reference values for the population and environment from which its patients are drawn, and make regular serial measurements in "longstay" members of the hospital staff to ensure the continuing reliability of the method and equipment used.

The applications of the method to the investigation of lung disease can be considered under three headings: (1) the identification of an environmental hazard and its early detection in individual subjects; (2) monitoring the progress of lung disease in relation to the need for or the response to treatment; (3) differential diagnosis.

Environmental hazards

A potential environmental hazard to the lungs may be identified in cross-sectional studies of an exposed group in comparison with a control group, while early detection of lung damage in individual subjects can be achieved by longitudinal studies. Carbon

Address for reprint requests: Dr Colin Ogilvie, Royal Liverpool Hospital, Liverpool L7 8XP.

monoxide transfer tests are appropriate for these purposes when the hazard is believed to have its earliest and main impact on the gas-exchanging tissues of the lung. Impaired carbon monoxide transfer, along with appropriate clinical signs and radiographic changes, is now accepted as one of the criteria for the recognition of asbestosis for purposes of industrial compensation. Impaired carbon monoxide transfer is also one of the earliest objective signs of an extrinsic allergic alveolitis. In the case of bird-fancier's lung, the impairment has been attributed to a reduced surface area for gas exchange and correlates with the duration of antigen exposure.[12] Longitudinal studies of carbon monoxide transfer may also help to exclude permanent or progressive pulmonary effects of a new environmental hazard; this was shown in the case of workers employed in the manufacture of biological detergents who suffered an asthmatic reaction to the inhalation of *Bacillus subtilis* but no lasting pulmonary damage as judged by serial measurements of carbon monoxide transfer.[13] It must be emphasised that carbon monoxide transfer, when expressed as overall "diffusing capacity" or "transfer factor," can be influenced by lack of co-operation and this is clearly relevant in the context of compensation for occupational lung disease. If the patient fails to make a complete expiration followed by a full inspiration before breath holding, a low value will be recorded. In these circumstances, as already mentioned, Kco can be calculated by dividing the overall result by the alveolar volume, but if alveolar volume varies greatly from one test to another a reliable value for carbon monoxide transfer cannot be obtained.

An important non-occupational environmental hazard is cigarette smoking. Carbon monoxide in cigarette smoke increases the back pressure of carbon monoxide in the blood, causing a small reduction in the values obtained for carbon monoxide transfer. This can be allowed for by measuring mixed venous carbon monoxide tension in a rebreathing procedure; but even when this is done smokers tend to have an impaired Kco owing mainly to a reduced pulmonary capillary volume—an effect which appears to be reversible.[14] It has been suggested that Kco is the most sensitive physiological test for the differentiation of smokers from non-smokers[15]; but in a recent longitudinal study of patients with emphysema smokers were better distinguished from ex-smokers by the fall in VC and FEV_1 than by the fall in Kco.[16]

Monitoring progress in relation to treatment

Serial measurements of carbon monoxide transfer may be used to monitor the progress of a lung disease. This information may be of prognostic value, help the clinician to decide when treatment is needed, and provide objective assessment of response to treatment. The test has been used for these purposes in various forms of diffuse interstitial lung disease, including sarcoid,[17] systemic sclerosis,[18] extrinsic allergic alveolitis,[12] and cryptogenic fibrosing alveolitis.[19] A fall in carbon monoxide transfer can sometimes be the earliest sign that the lungs are affected in these conditions and it has been taken as an indication for initiating immunosuppressive treatment or, in the case of allergic alveolitis, for removing the patient from further exposure to the relevant antigen. Even when these measures are taken, however, improvement in carbon monoxide transfer is often disappointing and rarely complete, suggesting that the fall does not take place until fibrosis is already established. In cryptogenic forms of fibrosing alveolitis carbon monoxide transfer does not correlate well with the activity or extent of the disease and is a poor guide to the likely response to treatment.[19] Possibly gallium scanning and the cytological examination of bronchial washings[20] will prove useful for these purposes, while changes in carbon monoxide transfer provide a quick and non-invasive measure of progress.

Certain drugs are known to induce lung damage, notably busulphan and bleomycin. Impairment of carbon monoxide transfer gives some indication of the frequency of such side effects and may be an early marker of lung damage. Only one of 23 patients treated with busulphan showed a significant fall in carbon monoxide transfer over a two-year period and this was the only patient to develop other evidence of lung damage.[21] By contrast, there was a fall in carbon monoxide transfer in 32 of 36 patients treated with bleomycin.[22] The impairment of carbon monxide transfer induced by bleomycin is linearly related to dose and may precede any spirometric or radiographic changes.[23] False-positive results may occur,[24] however, especially if appropriate corrections are not made for anaemia (see below).

Carbon monoxide is taken up by extravascular blood as well as by blood in the pulmonary capillaries. Increased carbon monoxide transfer has thus proved a useful marker of intrapulmonary haemorrhage in Goodpasture's syndrome[25,26] and also in vasculitic conditions, haemosiderosis, and thrombocytopenia.[27] In these conditions bleeding may occur at the capillary level, beyond the ciliary escalator, and may not show itself as haemoptysis. When carbon monoxide transfer is used to monitor patients susceptible to intrapulmonary haemorrhage, daily measurements are advised because carbon monoxide is not taken up by denatured haemo-

globin. A reversible rise in Kco of more than 50% above the baseline value is suggestive of bleeding into the lungs. This method of monitoring is more specific than radiography, less invasive than bronchial washings (for haemosiderin-laden macrophages), and less cumbersome than radioisotope techniques. Pulmonary haemorrhage may signal the onset of an exacerbation of the underlying disorder and its detection will permit the early institution of life-saving measures such as platelet transfusion or plasma exchange. A potential source of error in this and indeed other applications of the carbon monoxide transfer test is that it is effective as a monitor only when certain corrections have been made, notably for lung volume and haemoglobin concentration. The fall in lung volume which accompanies intrapulmonary haemorrhage contributes to but does not entirely account for the rise in Kco.. The correction made for anaemia also increases the value actually obtained for Kco and if, for example, the haemoglobin and carbon monoxide transfer measurements are not simultaneous a misleading result may occur.

Differential diagnosis

The patients most often referred to a pulmonary function laboratory for measurement of carbon monoxide transfer are those with diffuse pulmonary opacities. It is not generally appreciated that whereas the test may give some measure of the degree of dysfunction in these cases it is with few exceptions of no help in differentiating the various causes. One exception is the shadowing caused by recent intrapulmonary haemorrhage, which, as already stated, is accompanied by a high Kco; whereas in the conditions resembling it, such as pulmonary oedema and infections, the Kco is usually low. Assessing carbon monoxide transfer may also help to distinguish the shadows of a relatively inert dust from those of a fibrogenic dust; thus it is normal in most cases of simple coalworkers' pneumoconiosis, siderosis, and stannosis but reduced in silicosis and asbestosis.

The test is of more value in the differential diagnosis of certain conditions presenting with relatively clear lung fields, such as asthma and emphysema, pulmonary arterial hypertension, and intracardiac shunts. Although chronic obstructive lung disease can in theory influence carbon monoxide transfer in various ways (see above) reproducibility in stable cases is relatively good and similar to that of the FEV_1.[28] In general, it has been found that patients with the clinical features of asthma or chronic bronchitis but without radiographic evidence of emphysema have normal carbon monoxide transfer, while those with emphysema have a reduced value.[29–31] The large increase in alveolar volume in emphysema can mask this impairment of carbon monoxide transfer, especially if alveolar volume is obtained from multiple-breath helium dilution or body plethysmography. The result should therefore be expressed as the Kco rather than overall transfer factor (diffusing capacity). Most attempts to correlate the results of carbon monoxide transfer with histological proof of emphysema have been based on postmortem examination, which of necessity is carried out some time after the physiological studies. Both carbon monoxide transfer and flow-volume measurements, however, can detect even symptomless emphysema that is evident in surgical specimens removed immediately after the physiological studies were done.[32] The impairment of carbon monoxide transfer in emphysema tends to be greater than can be accounted for by loss of surface area alone. The fact that overall diffusing capacity increases with increasing breath-holding time in emphysema (but decreases in normal and asthmatic subjects) suggests that there is a resistance in the gas phase as well as in the diffusing membrane.[33]

Carbon monoxide transfer in asthma tends to be normal or even high[34 35] and so it is of particular value in discriminating between emphysema and asthma, especially the intrinsic late-onset form which can so closely mimic emphysema. The high diffusing capacity and Kco found in some cases of asthma has variously been attributed to overinflation with alveolar recruitment[36] and to an increase in pulmonary capillary volume due to maximal inspiration against obstructed airways.[35]

There are several pulmonary circulatory disorders in which carbon monoxide transfer can be abnormal even in the presence of radiographically clear lung fields. Primary pulmonary arterial hypertension,[37] thromboembolism,[38] and mitral valve disease[39] are generally associated with reduced carbon monoxide transfer due to reduced capillary volume, although in mitral disease impaired membrane diffusion from pulmonary oedema may play a part. In fact, carbon monoxide transfer is very variable in mitral disease because in the early stages the pulmonary capillary volume may actually be increased. (For this reason, the test is of little value in assessing either fitness for or response to mitral valve surgery.) On the other hand, reduced carbon monoxide transfer is a useful pointer to the diagnosis of pulmonary thromboembolism and decreasing values in successive samples of expirate collected during a single period of breath holding (because of the build-up of carbon monoxide back pressure in static blood) may prove to be a specific diagnostic test.[40] In contrast to these conditions, congenital heart disease with shunting of

Conditions in which the result of the carbon monoxide transfer test is normal, low, and high

Normal	*Low*	*High*
Thoracic cage disorders*	Diffuse interstitial lung disease (eg fibrosing alveolitis, asbestosis)	Polycythaemia
Pleural disease*	Sarcoidosis	Left-to-right shunt
Asthma	Emphysema†	Pulmonary haemorrhage (eg Goodpasture's syndrome)
Bronchitis	Pulmonary arterial hypertension	Asthma (some cases)
Localised pulmonary lesions	Pulmonary oedema	
Non-fibrotic pneumoconioses (eg coal, iron, tin)	Diffuse pneumonia	
	Smoking	
	Anaemia	

*D_L may be reduced; Kco is normal or high
†D_L may be normal; Kco is reduced.

blood from left to right is associated with increased carbon monoxide transfer, probably owing to recruitment of upper-lobe vessels, and this may gradually revert towards normal levels as pulmonary arterial hypertension supervenes.[41] Clearly therefore the carbon monoxide transfer test cannot provide a specific diagnosis in pulmonary circulatory disorders but an abnormal result, either high or low, may alert the clinician to a possible cause of unexplained dyspnoea or a radiographically abnormal pulmonary vasculature.

Finally, a normal value for carbon monoxide transfer is an essential requirement before dyspnoea is attributed to inorganic causes.

COLIN OGILVIE
Royal Liverpool Hospital
Liverpool

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Editorial note

Drs Forster and Ogilvie have been given freedom to express their ideas in their own language; but it should be noted that in Britain the terms "gas transfer factor" (TL) and "carbon monoxide transfer factor" (TLco) have replaced "diffusing capacity" (DL and DLco), and SI units have largely replaced traditional units.

Index	*SI units (x)*	*Traditional units (y)*	*Conversion factor (f) (ie y = fx)*
Gas transfer factor (TL, usually TLco)	mmol min^{-1} kPa^{-1}	ml min^{-1} $torr^{-1}$	2·986
Transfer coefficient (K, usually Kco)	mmol min^{-1} $kPa^{-1}]^{-1}$	min^{-1} $torr^{-1}$	2·986