

## Serial estimations of carbon monoxide diffusing capacity in intrapulmonary haemorrhage

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(Received 7 May/15 October 1980; accepted 8 January 1981)

### Summary

1. Serial estimations of the diffusing capacity for carbon monoxide, with a standard single-breath technique, were used to assist the monitoring of disease activity in patients at risk from intrapulmonary haemorrhage.

2. A reversible rise in diffusing capacity for carbon monoxide per unit alveolar volume ( $D_L\text{CO}/V_A$ ) of 50% or more above baseline values was detected on 61 occasions and in the diffusing capacity for carbon monoxide ( $D_L\text{CO}$ ) alone on 45 occasions in 39 patients.

3. Concurrent with these rises in  $D_L\text{CO}/V_A$  or  $D_L\text{CO}$ , two or more traditional indicators of intrapulmonary haemorrhage (haemoptysis, abrupt fall in haemoglobin concentration, chest X-ray opacities) were found on 47 occasions.

4. In the appropriate clinical context, acute reversible rises in  $D_L\text{CO}/V_A$  or  $D_L\text{CO}$  reflect active intrapulmonary haemorrhage.

**Key words:** alveolar volume, carbon monoxide, diffusing capacity, lung haemorrhage.

**Abbreviations:**  $D_L\text{CO}$ , diffusing capacity of the lung for carbon monoxide;  $D_L\text{CO}/V_A$ , diffusing capacity of the lung for carbon monoxide per unit alveolar volume;  $\text{FEV}_{1.0}$ , forced expiratory volume in 1 s;  $V_A$ , alveolar volume; VC, vital capacity.

### Introduction

The presence of intrapulmonary haemorrhage in severe thrombocytopenia or in a variety of

immunologically mediated conditions has previously proved difficult to detect. The haemoptysis is usually slight or absent (Azen & Clatanoff, 1964) because the source of bleeding is distal to the regions of mucociliary clearance. The radiographic changes of pulmonary haemorrhage are well recognized (Bowley & Steiner, 1979) but the X-ray appearance overlaps with that of pulmonary oedema or infection. In addition, the changes may persist for several days after bleeding has stopped. The finding of haemosiderin-containing macrophages in sputum specimens or bronchial lavage samples (Drew, Finley & Gole, 1977) or the accumulation of radioactivity in the lung after intravenous injections of  $^{51}\text{Cr}$ -labelled erythrocytes or  $^{59}\text{Fe}$  (Apt, Pollycore & Ross, 1957; Benoit, Dulon, Theil, Doolan & Watten, 1964) are methods which are too cumbersome or invasive for day-to-day monitoring.

The uptake of carbon monoxide (CO) by the lung is dependent on the number of haemoglobin-binding sites available for CO. In Goodpasture's syndrome, by using radioactive  $\text{C}^{15}\text{O}$  transient increases in the diffusing capacity for CO ( $D_L\text{CO}$ ) were shown to be caused by a stagnant pool of blood (Ewan, Jones, Rhodes & Hughes, 1976).

We report our experience of the use of serial estimations of  $D_L\text{CO}$  and diffusing capacity for CO per unit alveolar volume ( $D_L\text{CO}/V_A$ ) in the monitoring of disease activity in patients at risk from intrapulmonary haemorrhage.

### Subjects and methods

#### Patients

During the period 1975-1978, patients with pathological conditions associated with an

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increased risk of intrapulmonary haemorrhage were referred for standard pulmonary function tests by various specialist units within the Department of Medicine. Patients with thrombocytopenia were only referred if the likelihood of intrapulmonary haemorrhage was high. Patients with polyarteritis nodosa and Goodpasture's syndrome were routinely referred whether intrapulmonary haemorrhage was suspected or not. Tests were performed daily when active bleeding was suspected, but at less frequent intervals otherwise.

#### Pulmonary function tests

The forced expiratory volume in 1 s ( $FEV_{1.0}$ ) and the slow vital capacity (VC) were measured on a dry spirometer. Alveolar volume ( $V_A$ ) was determined by helium dilution during the measurement of the standard single breath  $D_LCO$  as set out by Cotes (1979). The  $D_LCO$  was corrected for haemoglobin concentration to a standard of 14.6 g/dl by applying the modification of Cotes, Dabbs, Elwood, Hall, McDonald & Saunders (1972) to the Roughton & Forster (1957) equation. The results for VC,  $D_LCO$  and  $D_LCO/V_A$  were expressed with reference to standard predicted values (Goldman & Becklake, 1959; Bradley, Bye, Hayden & Hughes, 1979). Two or three estimations of  $D_LCO$  and  $V_A$  were made at each laboratory attendance and the mean value was taken.

Estimations of  $D_LCO$  or  $D_LCO/V_A$  which were

50% or more above the predicted normal value for any patient were recorded. In addition, once baseline values of  $D_LCO$  and  $D_LCO/V_A$  were established on the basis of serial measurements, 50% rises above baseline were also recorded. Traditional indicators of intrapulmonary haemorrhage were also sought. The presence of fresh haemoptysis and of radiographic shadowing were recorded. The haemoglobin concentration was measured daily and falls of >1.5 g/dl in the absence of blood loss from the gastro-intestinal and genito-urinary tracts were taken as suggestive of intrapulmonary bleeding (Ewan *et al.*, 1976).

#### Results

Sixty-one episodes of large (>50% above baseline) and transient increases in  $D_LCO/V_A$  were detected in 39 patients. For each diagnostic group, the presence of haemoptysis, chest radiographic abnormalities, unexplained falls in haemoglobin concentration and the maximum levels in  $D_LCO$  as a percentage of the predicted and baseline values and  $D_LCO/V_A$  as a percentage of baseline are shown in Table 1. Haemoptysis or a combination of abnormal radiographic shadowing (Bowley & Steiner, 1979) and an unexplained fall in haemoglobin, accompanied the rise of  $D_LCO/V_A$  in 33 of 39 patients. Seven patients had two, six had three and one patient four such transient increases in  $D_LCO/V_A$ . On these 22 recurrent episodes, haemoptysis or a combi-

TABLE 1. Clinical details of patients

The diagnostic groups are shown with numbers of patients, mean ages, mean values for maximum diffusing capacity ( $D_LCO$ ) and diffusing capacity per unit alveolar volume ( $D_LCO/V_A$ ) as a percentage of the predicted and baseline values, and the number of patients showing a fall in haemoglobin concentration, haemoptysis and an abnormal chest radiograph.

Diagnosis	No. of patients	Age (years)	$D_LCO$ (% predicted)	$D_LCO$ (% baseline)	$D_LCO/V_A$ (% baseline)	No. of patients revealing		
						Fall in haemoglobin	Haemoptysis	Abnormal chest radiograph
Goodpasture's syndrome	21	34	126	197	240	16	10	17
Polyarteritis nodosa	4	47	124	176	190	3	2	3
Wegener's granulomatosis	4	48	118	155	183	3	2	4
Systemic lupus erythematosus	1	52	109	168	180	0	0	1
Glomerulonephritis	3	46	114	179	206	2	3	2
Idiopathic pulmonary haemosiderosis	1	12	122	193	244	1	0	1
Pulmonary oedema	2	47	90	154	171	1	2	2
Thrombocytopenia	3	54	104	148	195	1	2	2
Total (mean)	39	(40)	(120)	(182)	(219)	27	21	32

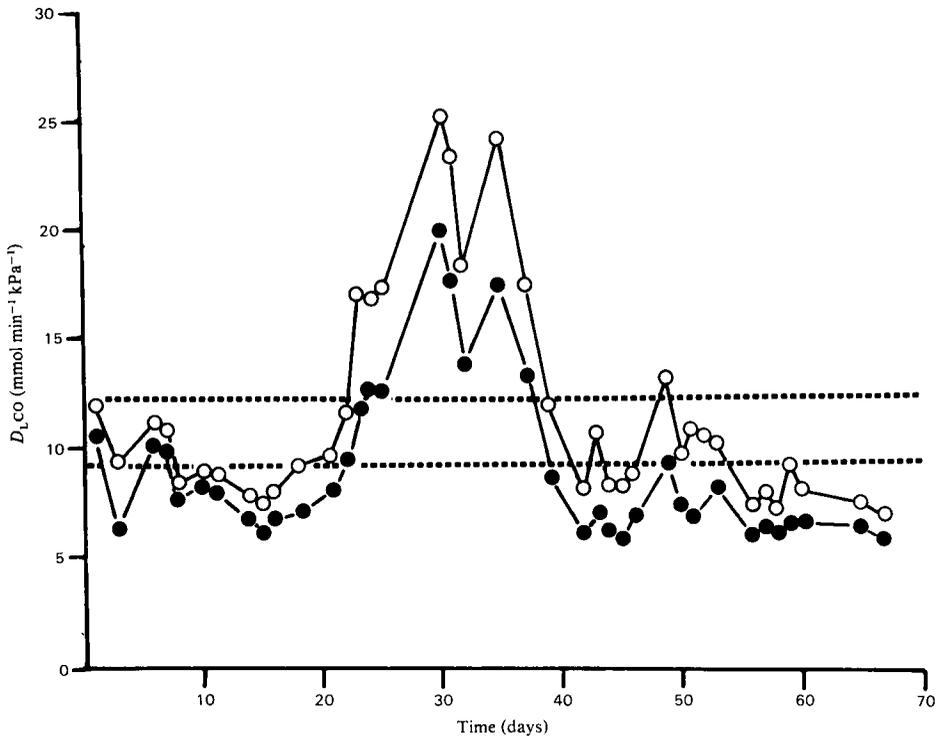


FIG. 1. Serial measurements of carbon monoxide diffusing capacity ( $D_{LCO}$ ) over a 70-day period in a patient with Goodpasture's syndrome with predicted range (mean  $\pm$  1 SD) indicated by dotted lines. The values with (O) and without ( $\bullet$ ) correction to a standard haemoglobin concentration of 14.6 g/dl are shown.

nation of abnormal radiographic shadowing and an unexplained fall in haemoglobin were observed on 19 occasions. Table 1 refers to the first and not the recurrent episodes. The individual results for all these variables on the first and recurrent episodes have been listed in *Clinical Science* Tables 80/4 and 80/5, which have been deposited with the Librarian, the Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE, who will supply copies on request.

Serial estimations of  $D_{LCO}$  in individual cases revealed discrete elevations. Fig. 1 shows  $D_{LCO}$  serially in a patient with Goodpasture's syndrome over a 70-day period; the elevations on days 30 and 35 were associated with haemoptysis and abnormal chest radiographs. The low baseline values were in keeping with his degree of renal failure (Lee & Stretton, 1975). The effect of the correction to a standard haemoglobin value (14.6 g/dl) can be seen.

The increases in  $D_{LCO}/V_A$  were greater than those in  $D_{LCO}$  (Figs. 2, 3). Nine patients failed to show a 50% or greater rise in  $D_{LCO}$  above baseline values at times when  $D_{LCO}/V_A$  achieved such a rise (compare the left lower quadrant in

each plot of Fig. 2); of these, seven had either haemoptysis or a combination of an abnormal chest X-ray and an unexplained fall in haemoglobin. Similarly, in the 22 recurrent transient increases of  $D_{LCO}/V_A$  the  $D_{LCO}$  rose by 50% or more on 15 occasions, but six of the remaining seven rises of  $D_{LCO}/V_A$  were accompanied by haemoptysis or by a combination of chest X-ray shadowing and a fall in haemoglobin.

Rises ( $\geq 50\%$ ) over predicted values for  $D_{LCO}$  or  $D_{LCO}/V_A$  were significantly less frequent than over baseline values, as shown in Fig. 2. Again,  $D_{LCO}/V_A$  was the more frequently elevated; in only five of 39 patients was peak  $D_{LCO}$  greater than 50% of the predicted value, compared with 24 of 39 patients for  $D_{LCO}/V_A$  (compare right upper quadrant in each plot of Fig. 2). At times of apparent intrapulmonary haemorrhage, changes were seen in other estimates of pulmonary function, such as  $FEV_{1.0}$ , VC and  $V_A$ . These were much smaller than the changes in  $D_{LCO}$  and  $D_{LCO}/V_A$  (Fig. 3).

The elevations of  $D_{LCO}/V_A$  usually lasted for several days (range 2–16 days: mean 8 days) after which the values returned to the baseline

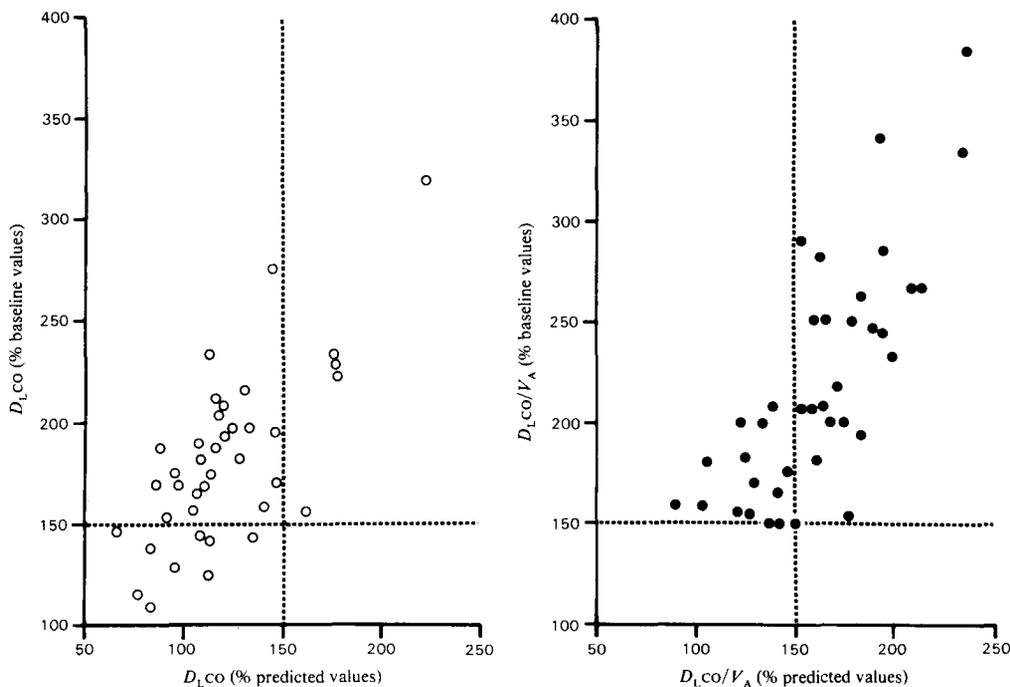


FIG. 2. Comparison of carbon monoxide diffusing capacity ( $D_{LCO}$ ) and carbon monoxide diffusing capacity per unit alveolar volume ( $D_{LCO}/V_A$ ) as percent predicted vs percent baseline levels, at times of maximum rise in the diffusing capacity in 39 patients. Dotted lines represent a rise of 50% above the baseline or predicted value.

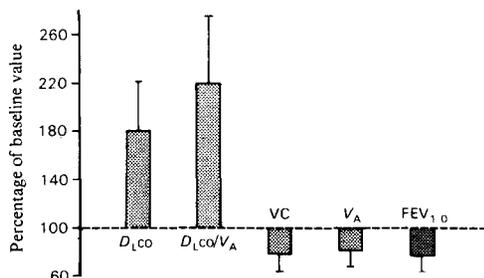


FIG. 3. Comparison of the maximum percentage change from baseline measurements of carbon monoxide diffusing capacity ( $D_{LCO}$ ), carbon monoxide diffusing capacity per unit alveolar volume ( $D_{LCO}/V_A$ ), forced expiratory volume in 1 s ( $FEV_{1.0}$ ), vital capacity (VC) and alveolar volume ( $V_A$ ) for 39 patients. Mean values and  $+1$  SD are shown.

values. Although this return to baseline was gradual (up to 11 days) in most patients, in three instances it was rapid, with a half-time averaging 1.7 days.

### Discussion

The association of acute rises in  $D_{LCO}/V_A$  (also referred to as  $K_{CO}$ ) with extravascular haemorrhage was shown in an earlier paper (Ewan *et al.*,

1976). Eight of the patients from that study are included in the present report. In view of the limited on-line availability of the MRC cyclotron, confirmation that the elevations of  $D_{LCO}$  and  $D_{LCO}/V_A$  described in the other 31 patients were caused by a stagnant pool of blood, by using radioactive carbon monoxide ( $C^{15}O$ ), was not sought. Nevertheless, the patients studied were known to be at risk from pulmonary haemorrhage by virtue of their clinical diagnoses and supporting evidence of bleeding, as judged by the presence of haemoptysis or a combination of abnormal X-ray shadowing and an unexplained fall in haemoglobin concentration, was present on 52 of the 61 episodes encountered. In addition, it must be extremely rare for conditions other than pulmonary haemorrhage to cause a large and reversible rise in the  $D_{LCO}$  in subjects who are at rest and who are always studied in the same posture. Nevertheless, a rise in cardiac output, if it occurred during pulmonary haemorrhage, might contribute to the rise in  $D_{LCO}/V_A$ .

As an indicator of pulmonary haemorrhage, a 50% rise above the predicted or baseline value was an arbitrary but conservative choice. By assuming an initial ratio between the membrane

conductance and the reactive conductance of 0.7, and a constant membrane conductance, a 50% increase in  $D_L\text{CO}$  according to the equation of Roughton & Forster (1957) implies a fourfold increase in pulmonary capillary blood volume, i.e. an extra 180–240 ml of blood in the lung. This is a conservative estimate because the membrane conductance for CO probably falls when blood is extravasated into the air spaces, making the contribution of the reactive conductance to the rise of  $D_L\text{CO}$  even greater. In a previous study of intrapulmonary haemorrhage (Ewan *et al.*, 1976), the presence of stagnant intrapulmonary blood, as assessed with  $\text{C}^{15}\text{O}$ , was always associated with a rise of 30% or more in the standard single breath  $D_L\text{CO}/V_A$ .

The intra-individual variance of  $D_L\text{CO}$  in our laboratory, on a day-to-day basis, is 5.4% in males and 7.9% in females; the variation between two measurements on a single day in our group of patients was less than 4%. In the absence of baseline measurements, a 50% increase of  $D_L\text{CO}/V_A$  above predicted is more than +2 SD above the predicted mean value in the younger age groups and +4 SD in the older age groups. In practice, the rise and fall of  $D_L\text{CO}$  (see Fig. 1) would appear to be more suggestive of active intrapulmonary haemorrhage than a single high estimation.

The falls in  $\text{FEV}_{1.0}$ , VC and  $V_A$  at times of suspected haemorrhage (Fig. 3) were of too small a magnitude to be helpful in themselves but, taken in conjunction with an acute rise in  $D_L\text{CO}/V_A$ , may prove to be of diagnostic value. The fall in  $V_A$  underlines the importance of monitoring  $D_L\text{CO}/V_A$  rather than  $D_L\text{CO}$ .  $D_L\text{CO}/V_A$  ( $K_{\text{CO}}$ ) and  $V_A$  are the primary measurements, so that a decrease in  $V_A$  reduces the actual increase of  $K_{\text{CO}}$ , when the derived expression  $D_L\text{CO}$  is used. The sensitivity of  $D_L\text{CO}/V_A$  is increased if baseline rather than predicted values are used as the reference point and if correction is made to a standard haemoglobin concentration (14.6 g/dl). Thus, when considering the 61 occasions on which there was a 50% or greater rise above baseline values of the standardized  $D_L\text{CO}/V_A$ , only two showed a 50% or greater rise over predicted values of the haemoglobin-uncorrected  $D_L\text{CO}$ .

After an acute episode of pulmonary haemorrhage the rate of decline of  $D_L\text{CO}$  and  $D_L\text{CO}/V_A$  is rapid, since the half-time for the fall to baseline levels was, on occasions, as short as 1.7 days. This reflects the fact that CO combines only with freshly released, intact haemoglobin molecules; in other words,  $D_L\text{CO}$  will be elevated only if CO is given before the extravasated haemoglobin has

undergone denaturation. This implies that if pulmonary haemorrhage is suspected the  $D_L\text{CO}$  should be measured at intervals of not more than 3 days and, preferably, daily. With less frequent estimations transient episodes of bleeding might be missed. Although the half-time for the fall to baseline levels was as short as 1.7 days, it was usually significantly longer. This presumably reflects a gradual cessation of bleeding rather than an abrupt stop.

Although the more traditional methods of detecting haemorrhage were frequently positive (Table 1), they may suffer from serious drawbacks. Haemoptyses can readily be missed if trivial or if the patient does not expectorate or collect all sputum. There is also evidence that pulmonary haemorrhage may occur in the absence of haemoptysis (Drew *et al.*, 1977). In addition, the expectoration of blood, shed in the periphery of the lung, is dependent on the time course of mucociliary clearance. Abnormal radiographic appearances are non-specific unless infection and oedema have been excluded (Bowley & Steiner, 1979). These appearances may persist for some time after cessation of active bleeding or may be absent or delayed (Bowley, Hughes & Steiner, 1979).

It is difficult to assess the sensitivity of  $D_L\text{CO}$  for pulmonary haemorrhage since, lung biopsy apart (and even this may be subject to sampling error), there is no absolute yardstick by which to judge its efficiency. On the other hand, the specificity of the test would appear to be good; reversible rises of 50% or more in the  $D_L\text{CO}$  or  $D_L\text{CO}/V_A$  when normal subjects or patients are examined at rest and in the same posture have yet to be recorded by this laboratory in circumstances other than those described here. Therefore serial estimations of  $D_L\text{CO}$  may be used in conjunction with traditional methods in monitoring intrapulmonary haemorrhage.

This series was biased towards life-threatening illnesses with renal involvement. Under more general circumstances, a greater percentage of patients with leukaemia and severe thrombocytopenia might have been seen. Nevertheless, this bias does not affect the need for a simple and reproducible test for detecting intrapulmonary bleeding since its early recognition may prompt changes in therapy, such as platelet transfusions or plasma exchange, which can be life-saving (Lockwood, Rees, Pearson, Evans, Peters & Wilson, 1976).

#### Acknowledgments

We are grateful to Mrs A. Watson, Mrs D. Hunter and Miss K. Patel for technical as-

sistance. We thank our colleagues in the Department of Medicine, and in particular Professor D. K. Peters, for referral of patients.

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