IRON-DEFICIENCY ANAEMIA: ITS EFFECT ON TRANSFER FACTOR FOR THE LUNG (DIFFUSING CAPACITY) AND VENTILATION AND CARDIAC FREQUENCY DURING SUB-MAXIMAL EXERCISE

J. E. COTES, J. M. DABBSS, P. C. ELWOOD, A. M. HALL, A. MCDONALD AND M. J. SAUNDERS

M.R.C. Pneumoconiosis Unit, Penarth, and Epidemiological Unit, Cardiff

(Received 22 July 1971)

SUMMARY

1. Measurements of transfer factor and sub-maximal exercise ventilation and cardiac frequency have been made on twenty women with iron-deficiency anaemia (Hb 8-9 g/100 ml) before and after ‘treatment’ with iron or placebo tablets and on control subjects.

2. The exercise ventilation, cardiac frequency and oxygen uptake were independent of haemoglobin concentration but the transfer factor was lower in the test than in control subjects and was increased by iron but not by placebo treatment. The results support the validity of the reaction-rate data for carbon monoxide with oxyhaemoglobin of Roughton & Forster (1957) despite evidence to the contrary from other studies.

3. In interpretation of sub-maximal exercise ventilation and cardiac frequency in iron-deficiency anaemia no allowance need be made for variation in haemoglobin concentration in the range 8-15 g/100 ml. For transfer factor a correction should be made by using a variant of the relationship of Roughton & Forster (1957).

Key words: anaemia, exercise, lung, cardiac frequency.

Iron-deficiency anaemia is usually evidence for decrease in total body haemoglobin and its subdivisions, including the amount of haemoglobin in pulmonary capillaries. The latter influences directly the overall pulmonary reaction rate for carbon monoxide with oxyhaemoglobin (Roughton & Forster, 1957); thus in anaemia the ability of the lung to absorb carbon monoxide and oxygen from the air and of the circulation to deliver oxygen to the muscles are both decreased.

The contribution to gas exchange may be studied by measurement of the transfer factor (diffusing capacity) for carbon monoxide (Tl). The dependence of this index on haemoglobin concentration has been confirmed by Rankin, McNeill & Forster (1961), Guleria, Pande, Markose, Gupta & Jain (1971), Burgess & Bishop (1963) and Herbert, Weill, Stuckey, Urner, Gonzales & Ziskind (1965) respectively for correction of acute anaemia by blood transfusion.

Correspondence: Dr J. E. Cotes, M.R.C. Pneumoconiosis Unit, Llandough Hospital, Penarth, Glamorgan.
and iron treatment and of polycythaemia by venesection. However, in the series for which complete data are available, also in the cross-sectional study of Dinakara, Blumenthal & Johnson (1970), the observed changes in $T_I$ are larger than predicted by the relationship of Roughton & Forster (1957) for the observed changes in haemoglobin concentration. Thus either the results for reaction rate are incorrect or, in the studies quoted, additional factors have contributed to the observed changes.

In relation to exercise, severe anaemia may be associated with profound disturbance of the cardiorespiratory response (Duke & Abelmann, 1969), but this appears to be diminished or absent with lesser degrees of anaemia as judged by measurements made during exercise performed before and after treatment (Beutler, Larsh & Tanzi, 1960; Andersen & Barkve, 1970). These authors studied a total of only nine patients and the measurements were sequential not contemporaneous.

For the present study the possibility of error in interpretation of the results owing to treatment with transfusion and/or venesection causing a change in the distribution of blood volume independent of haemoglobin concentration was avoided through correction of anaemia with oral iron, and possible systematic error due to the control observations preceding those after treatment was avoided by administration to some subjects of placebo tablets. In addition the findings were compared with those for other subjects drawn from the same community. The findings throw light on the validity of estimates of the reaction rate of carbon monoxide with oxyhaemoglobin in man and the allowance which should be made for haemoglobin concentration in interpretation of tests of respiratory and cardio-muscular function.

**METHODS**

The subjects were adult women living in Barry, Glamorgan. They were identified during an epidemiological survey and comprised all those found to have a circulating haemoglobin concentration of less than 9.5 g/100 ml. The subjects were carefully questioned as to their symptoms and further investigations were arranged as indicated. From these it became apparent that the cause of the anaemia was usually iron deficiency associated with menorrhagia (cf. Elwood, Rees & Thomas, 1968). All subjects had normal chest X-rays and lung function and were free from airway obstruction. They agreed to take part in the study after its nature had been explained and the general practitioner had been informed. Measurements were made before and 2 months after treatment four times daily with tablets containing either lactose or stabilized ferrous carbonate (daily dosage of Fe 200 mg); but for some subjects the results after treatment were incomplete. Allocation of treatment with iron or placebo was made in the ratio of 3 to 2 by using a double-blind randomized procedure; those who received the placebo were subsequently given a second course of treatment with iron.

The results were compared with those for control subjects aged 45–55 years who were drawn by a process of random sampling from the population of a near-by rural area in the Vale of Glamorgan.

Respiratory symptoms were investigated by using the Medical Research Council Questionnaire (1966) and forced expiratory volume and vital capacity by using a bellows spirometer (McDermott, McDermott & Collins, 1968).

The transfer factor was measured in an upright posture by the single breath carbon monoxide method at oxygen tensions of approx. 110 and 600 Torr by using a semi-automatic apparatus
Lung function in iron-deficiency anaemia

(Meade, Saunders, Hyett, Reynolds, Pearl & Cotes, 1965). The alveolar volume during breath holding was determined from the dilution in the lung of helium contained in the test breath, and the components of transfer factor, the diffusing capacity of the alveolar membrane ($Dm$) and volume of blood in alveolar capillaries ($Vc$) were derived in a standard manner (Cotes, 1968). These results were then used to calculate the $Dm/Vc$ ratio. The blood haemoglobin concentration was determined by the cyanmethaemoglobin method using an EEL Haemoglobinometer on blood drawn from an antecubital vein; total body haemoglobin was measured by the carbon monoxide method (Ekelund, 1965). For the latter measurement the subject, after breathing oxygen in open circuit, rebreathed from a closed circuit apparatus containing 95% O$_2$ and 5% He. These concentrations were maintained by absorption of carbon dioxide and addition of oxygen at the rate at which it was utilized by the subject. In these circumstances a constant helium concentration was evidence for absence of gas leaks into or out of the apparatus. Carbon monoxide (18 ml) was added to the circuit at 20 min and measurements of carbon monoxide concentration for calculation of haemoglobin saturation with carbon monoxide were made just before this time and again 20 min later.

Exercise with the legs was undertaken by the subjects seated upright on a cycle ergometer (Lanooy). The test subjects cycled for two consecutive periods of 4 min at 30 and 60 W, with a single period of rebreathing for determination of the tension of carbon dioxide in mixed venous blood during the fourth minute. For the control subjects the rate of work was increased by 10 W/min and no period of rebreathing was attempted. But in a subsequent study a further group of control subjects reproduced the pattern of exercise undertaken by the test subjects. Ventilation minute volume (by gas meter) and cardiac frequency (by continuously running ECG) while breathing air were recorded for the test subjects during the second and third minutes at each work level and for the control subjects continuously for each minute of exercise. Oxygen uptakes were calculated from these results and graphs constructed for ventilation minute volume and cardiac frequency against oxygen uptake. Then best fitting lines were drawn by eye and used for derivation of the ventilation minute volume and cardiac frequency at the oxygen uptakes of 1.0 and 0.75 l/min ($V_E,1.0$ and $V_E,0.75$ and $CF,1.0$ and $CF,0.75$ respectively). The equipment and procedure are described in detail by Cotes (1971). Rebreathing, for estimation of mixed venous carbon dioxide tension, was of 10 s duration and was carried out with the rebreathing bag containing initially 1.5 l of 11% CO$_2$ in 28% O$_2$. The gas was sampled continuously at the lips and the concentration registered on a Mingograf recorder. For this purpose the sampling distance from the mouthpiece to the infra red CO$_2$ detector (Hartman and Braun URAS3) was 25 cm, when the lag time for the analyser was 70 ms and the response time 110 ms. The CO$_2$ plateaux during rebreathing were scrutinized for their technical quality and those that were satisfactory were accepted. In the event results were obtained for only twelve of the twenty test subjects and, for these, calculation of cardiac output was made by the method of Denison (1967) by using the measured CO$_2$ output during the third minute of exercise, the end-tidal $P_{CO_2}$ at the start of the fourth minute, the CO$_2$ plateau during rebreathing and the CO$_2$ dissociation curve of Dill, Edwards & Consolazio (1937).

RESULTS

Information about the subjects is listed in Table 1. This shows that the test subjects on their first attendance differed from the others in having a lower haemoglobin concentration and total
body haemoglobin. The ventilatory capacities were similar between the groups but the anaemic subjects had rather larger residual volumes (Table 2). The transfer factor and KCO (transfer factor/litre of lung volume) were significantly lower for the anaemic subjects than the controls whereas the \( Dm/Vc \) ratio was increased.

**Table 1. Relevant information about the subjects: mean values and ranges**

<table>
<thead>
<tr>
<th></th>
<th>Test subjects</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.8 (33–65)</td>
<td>48.6 (45–54)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.58 (1.48–1.69)</td>
<td>1.59 (1.46–1.72)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.4 (36.4–79.5)</td>
<td>66.3 (47.3–107.1)</td>
</tr>
<tr>
<td>Hb concentration (g/100 ml)</td>
<td>8.6 (5.8–10.2)</td>
<td>14.2 (12.8–15.6)</td>
</tr>
<tr>
<td>Total Hb* (g)</td>
<td>338 (212–438)</td>
<td>529 (389–712)</td>
</tr>
<tr>
<td>Grade of activity†</td>
<td>1.3 (0–3)</td>
<td>1.4 (0–3)</td>
</tr>
</tbody>
</table>

* This measurement was made on eleven and twelve subjects respectively.
† On four point scale.

**Table 2. Data for lung function: mean values and ranges**

<table>
<thead>
<tr>
<th></th>
<th>Test subjects</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forced expiratory volume (FEV) (l)</td>
<td>2.29 (1.46–3.35)</td>
<td>2.35 (1.65–3.40)</td>
</tr>
<tr>
<td>Forced vital capacity (FVC) (l)</td>
<td>3.09 (1.80–4.23)</td>
<td>3.04 (2.30–4.90)</td>
</tr>
<tr>
<td>((FEV \times 100)/FVC) (%)</td>
<td>73.9 (66.0–85.7)</td>
<td>77.3 (69.4–85.5)</td>
</tr>
<tr>
<td>Residual volume (RV') (l)</td>
<td>*1.99 (1.42–2.82)</td>
<td>1.74 (1.29–2.29)</td>
</tr>
<tr>
<td>Transfer factor (( Tl' )) (ml min(^{-1}) Torr(^{-1}))</td>
<td>*21.2 (9.2–31.9)</td>
<td>26.3 (19.6–32.4)</td>
</tr>
<tr>
<td>KCO (( Tl'/\text{alveolar volume} )) (min(^{-1}) Torr(^{-1}))</td>
<td>*4.26 (2.7–5.4)</td>
<td>5.7 (4.5–7.2)</td>
</tr>
<tr>
<td>( Dm/Vc ) (min(^{-1}) Torr(^{-1}))</td>
<td>*1.38 (0.52–3.9)</td>
<td>0.70 (0.42–1.05)</td>
</tr>
</tbody>
</table>

\( Dm \) is diffusing capacity of alveolar membrane and \( Vc \) volume of blood in alveolar capillaries.
* \( P<0.05 \).

The mean results for sub-maximal exercise (Table 3) show that exercise ventilation, cardiac frequency and oxygen uptake are similar for the test and control subjects. The indirectly determined cardiac outputs of the test subjects are similar to those reported for normal subjects in the literature (Reeves, Grover, Blout & Filley, 1961).

The mean changes in physiological function of the test subjects after treatment with iron or placebo tablets (Table 4) show that, compared with placebo treatment, iron treatment was associated with significant increases in haemoglobin concentration, total body haemoglobin, transfer factor and KCO, also a decrease in oxygen uptake during the third minute of exercise.
at 30 W. Between the two treatment groups no significant changes were observed for the ventilation and cardiac frequency standardized for oxygen uptake. However, taking the two treatment groups together significant changes \((P < 0.05)\) occurred between the first and second occasions with respect to the exercise cardiac frequency (which was decreased on average by 6 beats/min) and the \(Dm/Vc\) ratio; the latter change was associated with a significant increase of 14 ml in the

**TABLE 3. Results for sub-maximal exercise: mean values and ranges or standard deviation**

<table>
<thead>
<tr>
<th>Test subjects</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation at (\dot{V}O_2,1.0) l/min ((\dot{V}E,1.0) (l/min)</td>
<td>27.1 (23.5–34.0)</td>
</tr>
<tr>
<td>Cardiac frequency at (\dot{V}O_2,1.0) l/min (CF,1.0) (beats/min)</td>
<td>133 (110–160)</td>
</tr>
<tr>
<td>Cardiac output* at (\dot{V}O_2,1.0) l/min ((Q_t,1.0)) (l/min)</td>
<td>9.6 (SD 2.9)</td>
</tr>
<tr>
<td>Oxygen uptake at 30 W ((\dot{V}O_2,30)) (l/min)</td>
<td>0.87 (0.65–1.18)</td>
</tr>
</tbody>
</table>

\(\dot{V}O_2\) is oxygen uptake and \(\dot{V}E\) expired minute volume.

* From linear regression for pooled results.

† These results relate to other subjects mentioned in the text.

**TABLE 4. Change in lung function and response to exercise in subjects with low haemoglobin concentration after treatment with iron or placebo tablets. The numbers of subjects are given in parentheses**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Iron</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb concentration (g/100 ml)</td>
<td>+4.4* (12)</td>
<td>−0.6 (8)</td>
</tr>
<tr>
<td>Total Hb (g)</td>
<td>+104* (6)</td>
<td>−21 (5)</td>
</tr>
<tr>
<td>Tl (ml min(^{-1}) Torr(^{-1}))</td>
<td>+3.4* (12)</td>
<td>−0.4 (8)</td>
</tr>
<tr>
<td>KCO (min(^{-1}) Torr(^{-1}))</td>
<td>+0.73* (12)</td>
<td>+0.2 (8)</td>
</tr>
<tr>
<td>(Dm/Vc) (min(^{-1}) Torr(^{-1}))</td>
<td>−0.46† (12)</td>
<td>−0.53† (8)</td>
</tr>
<tr>
<td>(\dot{V}O_2) at 30 W (l/min)</td>
<td>−0.15* (8)</td>
<td>−0.01 (4)</td>
</tr>
<tr>
<td>(\dot{V}E) at (\dot{V}O_2,0.75) (l/min)</td>
<td>+1.6 (9)</td>
<td>−0.3 (3)</td>
</tr>
<tr>
<td>CF at (\dot{V}O_2,0.75) (beats/min)</td>
<td>−6† (9)</td>
<td>−7† (3)</td>
</tr>
<tr>
<td>(Q_t) at (\dot{V}O_2,0.75) (l/min)</td>
<td>−0.8 (4)</td>
<td>—</td>
</tr>
</tbody>
</table>

For definitions of symbols see Tables 2 and 3.

* Difference associated with treatment \((P < 0.05)\).

† Difference differs from zero \((P < 0.05)\).

volume of blood in the alveolar capillaries. The reproducibility of components of the measurement of transfer factor is given in Table 5.

The mean results for transfer factor before and after treatment are shown in relation to haemoglobin concentration in Fig. 1 which also shows the relationship of transfer factor to
haemoglobin concentration calculated by using the relationship of Roughton & Forster (1957):

\[
\frac{1}{T_1} = \frac{1}{Dm} + \frac{1}{\theta [\text{Hb}] Vc}
\]

where \( \theta \) is the reaction rate of carbon monoxide with oxyhaemoglobin and \([\text{Hb}]\) is haemoglobin concentration as a fraction of the arbitrarily chosen reference value of 14.6 g/100 ml. In the calculation the values used for \( Dm \) and \( Vc \) were the means observed for the normal population from whom the present control subjects were drawn (Cotes & Hall, 1970). Fig. 1 shows that the

\begin{table}
\begin{tabular}{lll}
\hline
 & Mean & SD & Coefficient of variation \\
\hline
Alveolar volume (l) & 4.96 & 0.29 & 5.9 \\
Time of breath holding (s) & 9.11 & 0.74 & 8.2 \\
Volume of washout (l) & 0.762 & 0.09 & 11.7 \\
Volume of sample (l) & 0.831 & 0.12 & 14.1 \\
\hline
\end{tabular}
\end{table}

Fig. 1. Observed mean results and predicted regression relationship of lung transfer factor for carbon monoxide on haemoglobin concentration for female subjects before and after treatment of anaemia. ×, Treated with iron; ○, placebo treated.

initial values for transfer factor in the anaemic subjects are similar to those expected for control subjects having the same haemoglobin concentration, whereas the increase in transfer factor after correction of anaemia is that to be expected from the known properties of \( \theta \).
DISCUSSION

The increase in haemoglobin concentration and total body haemoglobin in the test subjects who received iron, and the small non-significant decrease in those who received placebo tablets provided a basis for comparison of the response to treatment which was unbiased by possible placebo effects. In addition the existence of an external control group permitted an assessment of whether or not the test subjects were in other respects typical of the population of which they formed a part.

The method adopted for reporting the exercise ventilation and cardiac frequency effectively made allowance for the different procedure for exercise of the test and control subjects (Cotes, Allsopp & Sardi, 1969). Its validity in the present circumstances was further confirmed by the results of study of the second control group to which reference is made in the Methods section. This group also provided a value for oxygen uptake at 30 W which was for practical purpose identical with that in the test subjects (Table 3). In addition for the latter, correction of the anaemia had only a small effect on oxygen uptake in the direction of a decrease and not an increase. This change is compatible with increased familiarity with the procedure (cf. Cotes & Meade, 1959) and together with the initial values provides no support for the view that a decrease of oxygen uptake in relation to rate of work is one of the mechanisms whereby the body adapts to a decrease in body haemoglobin concentration (Sproule, Mitchell & Miller, 1960).

The ventilation of the test subjects during sub-maximal exercise was the same as that of the controls and was influenced neither by repetition after treatment with placebo tablets nor by correction of anaemia with iron. This observation confirms those cited above. The sub-maximal exercise cardiac frequency was likewise similar for the test and control subjects but was lower after correction of anaemia with iron. The change might have been attributed to the treatment had not a similar change occurred after placebo tablets (Table 4). This placebo effect indicates the need for appropriate control observations. These confirm that as well as the exercise ventilation the exercise cardiac frequency is uninfluenced by haemoglobin concentration in the range 8–15 g/100 ml. This finding has an important application in the interpretation of test results for sub-maximal exercise. In addition, we find no evidence for an increase in cardiac output. Thus the results support the view that moderate iron-deficiency anaemia is compensated for mainly by a decrease in mixed venous oxygen saturation and associated shift to the right of the oxygen dissociation curve (e.g. Edwards, Novy, Walters & Metcalfe, 1968). More marked anaemia may be accompanied by tachycardia, an increase in cardiac stroke volume and hypotension associated with hypovolaemia. But these abnormalities are apparently corrected by a modest increase in haemoglobin concentration (e.g. from 5·9 to 10·9 g/100 ml; Duke & Abelmann, 1969).

In contrast with exercise, the transfer factor for carbon monoxide is influenced to a material extent by fluctuations in haemoglobin concentration. This observation has important implications for interpretation of data both on the reaction rate of carbon monoxide with oxyhaemoglobin and on the transfer factor in subjects with an unusual haemoglobin concentration. In the circumstances of the present study the relationship between the variables is reproducible, is not
associated with any placebo effect and may be fully accounted for in terms of the reaction rate for carbon monoxide with oxyhaemoglobin of Roughton & Forster (1957) which is haemoglobin dependent. This finding differs from those cited in the introduction where, after alteration in haemoglobin concentration, a larger-than-predicted change in transfer factor was observed. The evidence is summarized in Table 6. But in the anaemic patients studied by Rankin et al. (1961) the measurements before transfusion were made during weakness or shock after acute blood loss, hence the initial transfer factor was possibly unduly low. By contrast, for the

Table 6. Effects on pulmonary transfer factor of blood transfusion in patients with acute anaemia and of venesection in patients with polycythaemia. Results are from (1) Rankin et al. (1961), (2) Burgess & Bishop (1963), (3) Herbert et al. (1965). The values calculated for TI after treatment are based on the initial TI, the haemoglobin concentrations, the relationship for 1/θ of Roughton & Forster (1957) and Dm and Vc before treatment or in the case of (3) an assumed Dm/Vc ratio of 0.7. The values predicted for TI are for (1) those of Ogilvie et al. (1957) and for (2) and (3) of Cotes (1968).

<table>
<thead>
<tr>
<th></th>
<th>Anaemia (acute)</th>
<th>Polycythaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1)</td>
<td>Vera (2)</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Before treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb (g/100 ml)</td>
<td>6.0</td>
<td>19.3</td>
</tr>
<tr>
<td>TI (ml min⁻¹ Torr⁻¹)</td>
<td>11.1</td>
<td>28.7</td>
</tr>
<tr>
<td>After treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb (g/100 ml)</td>
<td>10.9</td>
<td>14.5</td>
</tr>
<tr>
<td>Observed TI (ml min⁻¹ Torr⁻¹)</td>
<td>17.3</td>
<td>20.2*</td>
</tr>
<tr>
<td>Calculated TI (ml min⁻¹ Torr⁻¹)</td>
<td>13.8</td>
<td>24.8*</td>
</tr>
<tr>
<td>TI predicted from normal values</td>
<td>24.1</td>
<td>25.6</td>
</tr>
</tbody>
</table>

* P<0.05; † for pooled results P<0.02.

patients with polycythaemia, studied by Burgess & Bishop (1963) and by Herbert et al. (1965), the transfer factor after venesection was less than expected (hence the decrease due to venesection was enhanced, P<0.05) possibly on account of the subjects also having had thrombotic episodes in the pulmonary circulation, the effects of which were previously compensated by an increase in pulmonary blood volume and uncovered when the blood volume was restored to normal. The present results are free from these complicating factors since the subjects had both normal pulmonary function and blood volumes and the changes in haemoglobin concentration were effected gradually by administration of iron.

Our results suggest that the value of Roughton & Forster (1957) for θ effectively defines the steady-state relationship of transfer factor to haemoglobin concentration. Thus it may be used to correct the transfer factor for deviations from normal concentration. To this end, when results for Dm and Vc are available, the standardized TI (i.e. TI_s at haemoglobin concentration 14.6 g/100 ml and alveolar capillary oxygen tension 110 Torr) may be obtained by use of eq.
Lung function in iron-deficiency anaemia

1) with \( \theta \) unity. When \( T1 \) results are available only for breathing air the correction may still be made provided a value is assumed for the \( Dm/Vc \) ratio. It can then be shown that:

\[
T1,s = T1,obs \left(14\cdot6a + Hb\right) \cdot (1 + a)[Hb]
\]

where \( T1,s \) and \( T1,obs \) are the standardized and observed values for transfer factor, \( a \) is the \( Dm/Vc \) ratio and \([Hb]\) is haemoglobin concentration. For the present control subjects and for the test subjects after treatment the \( Dm/Vc \) ratio (\( a \)) is approx. 0.7 and the average relationship fits the data well (Fig. 2). It may be used routinely in this form except when the \( Dm/Vc \) ratio is likely to be abnormal. This appeared to be the case for the test subjects before treatment in whom on account of a low value for Vc the \( Dm/Vc \) ratio was initially 1.4. On repetition of the measurements the ratio fell towards the control value (Table 4); this change was unrelated to changes in blood volume. The change does not appear to be technical since, on account of the time taken for the study, measurements made before treatment in some subjects coincided with those made after treatment in others and the results were technically comparable between the two occasions (Table 5). Nor was it due to correction of the anaemia since it occurred for the subjects who received placebo tablets as well as those who received iron. It could theoretically have been due to a relative hypotension at the time of first measurement but blood pressure was not recorded, so this hypothesis cannot now be confirmed. Alternatively, the control results might be incorrect but similar values have been observed both by Frans (1970) for normal subjects of the age and size of the present test subjects and by ourselves (unpublished work) for

---

**Fig. 2.** Results for nineteen subjects (range of Hb concentration 6.6-14.7 g/100 ml) showing relationship between standard \( T1(T1,s) \) by using correction factor and observed \( Dm \) and Vc.
subjects with moderate iron-deficiency anaemia in New Guinea. Thus the explanation for the
results before treatment remains unclear.

The findings may be contrasted with those for patients with either more-marked iron-
deficiency anaemia (Rankin et al., 1961; Guleria et al., 1971) or sickle-cell anaemia (Miller &
Serjeant, 1971; Femi-Pearse, Gazioglu & Yu, 1970) in whom the Dm/Vc ratio was decreased on
account of low values for Dm which were in some instances compensated for by high values for
Vc. This lability of the ratio emphasizes the desirability of making a full allowance for variation
in haemoglobin concentration by measurement of Dm and Vc wherever possible.

The Dm/Vc ratio is determined in part by the value chosen for the constant term (a) in the
regression of θ on oxygen tension, where a reflects the gas permeability of the erythrocyte
membrane relative to that of the cell interior (λ). In the present study λ has been assumed to be
infinite (Cotes, 1968). This assumption, although not materially influencing the usefulness of the
index, has the effect of improving the reproducibility of Dm (Cotes & Hall, 1970) relative to
that with a lower and possibly more-accurate value for λ (Holland, 1969). However, the assumption
has the effect that the Dm/Vc ratio may have been under-estimated and the correction for
haemoglobin concentration over-estimated in consequence. In an attempt to resolve this
uncertainty the relationship of Roughton & Forster (1957) has been rearranged and solved for
λ by using the present results. The mean result so obtained is compatible with a value for λ for
infinity but the confidence limits are too wide for any reliance to be placed on the result. Thus
the ‘best’ correction factor for transfer factor of haemoglobin concentration has still to be
established; it is unlikely to deviate greatly from that suggested here.

Meanwhile the present results for sub-maximal exercise, although relevant to the circum-
stances in which they were obtained, should not be extrapolated to more strenuous exercise or
more-marked anaemia. On these topics, as on the correction of transfer factor for haemoglobin
concentration, there is still need for further work.

ACKNOWLEDGMENT

We are indebted to Dr J. C. Bignall and other colleagues for the medical assessment of our
subjects’ anaemia.

REFERENCES

Clinical and Laboratory Investigation, 25, Suppl. 114, 3–62.

BEUTLER, E., LARSH, S. & TANZI, F. (1960) Iron enzymes in iron deficiency. VII. Oxygen consumption measure-


COTES, J.E. (1968) Lung Function: Assessment and Application in Medicine, 2nd edn. Blackwell Scientific Publica-
tions, Oxford.

COTES, J.E. (1972) Assessment and interpretation of the physiological response to sub-maximal exercise: use of a

progressive and steady-state exercise, between arm and leg exercise, and between subjects differing in body

Lung function in iron-deficiency anaemia


