IRON-DEFICIENCY ANAEMIA: ITS EFFECT ON MAXIMUM AEROBIC POWER AND RESPONSES TO EXERCISE IN AFRICAN MALES AGED 17–40 YEARS

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SUMMARY

1. The physiological responses to exercise of two groups of industrial workers with moderate and severe anaemia were measured and compared with a group of matched controls, working and living under similar conditions. Exercise was performed on a stationary bicycle ergometer at five consecutive work loads. During the final minute of each exercise period, oxygen intake, minute ventilation volume, and cardiac and respiratory frequencies were measured. On a separate occasion, blood haemoglobin concentration was measured at rest and cardiac output and blood and plasma volumes were estimated while subjects exercised at a fixed percentage of the maximum aerobic power for 6 min.

2. Oxygen intake for a given work load and ventilation rate was similar in all subjects studied but exercise cardiac output was elevated in the anaemic group. The increased cardiac output was due to an increased heart rate, the stroke volume being similar in the anaemic and control subjects. There was a marked decrement (~34%) in maximum aerobic power and some evidence of a raised plasma volume in the severely anaemic group.

3. These results suggest that anaemia impairs performance during moderate and near maximum exercise. There is an associated rise of cardiac output and plasma volume.

Key words: anaemia, oxygen consumption, exercise, cardiac output.

There have been few studies of the physiological responses to exercise of anaemic subjects and the evidence from these is conflicting. Beutler, Larsh & Tanzi (1960), for instance, report that during exercise the transport of oxygen to the working tissues is unaffected by a decrease in haemoglobin concentration, whereas Sproule, Mitchell & Miller (1960) show clearly that severe anaemia produced a large decrement (>50%) of maximum aerobic power ($\dot{V}O_2_{max}$).

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These authors also reported that the anaemic subjects are able to exercise at similar levels of maximum work (despite their reduced \( \dot{V}O_2,_{\text{max}} \)) as the controls without signs of symptomatic stress. This may mean that severe anaemia results in the greater utilization of anaerobic sources of energy during work. However, the authors presented no evidence on this point, and their work has not been confirmed by the recent studies of Cotes, Dabbs, Elwood, Hall, McDonald & Saunders (1972). They, like Beutler and his co-workers (1960), found no evidence that moderate anaemia (Hb = 8.6 g/100 ml) either impaired work performance or was associated with compensatory cardiovascular adjustments.

In the present investigation we have attempted to resolve these differences in experimental observations, by comparing the cardiovascular responses and exercise tolerance of two groups of industrial workers with moderate (Hb = 8-10 g/100 ml) and severe (Hb < 8 g/100 ml) anaemia with matched normal controls (Hb > 13 g/100 ml) working and living under similar conditions.

MATERIALS AND METHODS

The subjects were African industrial workers living and working in Dar es Salaam. Their physical characteristics together with circulating haemoglobin levels are given in Table 1.

The subjects were identified during an epidemiological survey of industrial anaemia. The severe anaemic group comprised all those found with a haemoglobin concentration of less than 8 g/100 ml. Those with moderate anaemia (Hb = 8-10 g/100 ml) were randomly selected from a group of 200 workers. Each subject in groups II and III (Table 1) was matched approximately with a normal control (Hb > 13 g/100 ml) on the basis of age, weight, height, job and place of work, the aim being as far as possible to use work-mates performing identical tasks in the same factory. All subjects were examined clinically and a chest X-ray and lung-function tests were performed. If they were free of symptoms (except those arising from the anaemia), the nature of the experiment was explained to them and, if they agreed, they were included in the study.

The subjects attended the laboratory on a single occasion. During the preliminary session they were allowed to become familiar with the procedures (Davies, Tuxworth & Young, 1970). Following this period the subjects were then required to exercise for five consecutive 3 min
periods at 180, 360, 540, 720 and 900 kpm/min. During the final minute of each period oxygen intake (\(\dot{V}_O_2\)), minute ventilation (\(\dot{V}_E\)), cardiac (\(\dot{f}_H\)) and respiratory (\(\dot{f}_R\)) frequencies were measured. Finally, after a 1 h rest-period haemoglobin concentration was measured at rest and cardiac output (\(Q\)), blood (\(V_b\)) and plasma (\(V_p\)) volumes, \(\dot{V}_O_2\) and \(\dot{f}_H\) determined with the subjects exercising at a fixed (~60%) percentage of their maximum aerobic power as judged from their previous work performance.

Minute ventilation and \(\dot{V}_O_2\) was measured using a standard open circuit technique previously described (Davies, 1968). The subjects breathed through a low-resistance Otis–McKerrow valve and expired air, collected into Douglas bags, was analysed for \(O_2\) and \(CO_2\) content using a paramagnetic Servomex \(O_2\) analyser and a katherometer. These instruments were calibrated at frequent intervals using standard gas mixtures previously analysed by the Lloyd–Haldane chemical method. The accuracy of these techniques has been previously reported (Davies & Shirling, 1967). Cardiac frequency was determined from a continuous recording of the electrocardiogram. For measurement of blood and plasma volumes a 2% solution of Evans Blue containing approximately 3 mg of dye was injected into an ante-cubital vein of the left arm and samples were withdrawn from the right arm after 5, 10 and 15 min. A straight line was fitted by eye to the semi-logarithmic plot of dye concentration against time and the theoretical concentration of dye at zero time was estimated by extrapolation. Blood and plasma volumes were then derived in the standard way. The blood haemoglobin concentration was determined by the cyanmethaemoglobin method using an EEL photometer; duplicate measurements were required to agree within \(\pm 0.5 \, g/100 \, ml\). Cardiac output was estimated by the indirect Fick technique using an ear oximeter. Oxygen intake was calculated from ventilatory and expired gas data and individual regression lines were fitted by the method of least squares to plots of minute ventilation volume and cardiac frequency on \(\dot{V}_O_2\), and to \(\dot{V}_O_2\) on work load and cardiac frequency. From these data, \(\dot{V}_O_2\) was expressed at a fixed work load of 900 kpm/min (\(\dot{V}_O_2, 900\); and maximum aerobic power (\(\dot{V}_O_2, \text{max}\)) was predicted from an extrapolation of the fitted \(\dot{f}_H/\dot{V}_O_2\) line to a cardiac frequency of 195 beats/min. Minute ventilation volume and cardiac frequency were expressed at a \(\dot{V}_O_2\) of 1.5 litres/min (\(\dot{V}_1.5\) and \(\dot{f}_H, 1.5\)) respectively (see Cotes, Davies, Edholm, Healey & Tanner, 1969).

RESULTS
The blood and plasma volumes of the anaemic subjects and their controls are given in Table 1. The responses to submaximal exercise are summarized in Table 2 and Figs. 1–3. The severely (mean Hb = 6.7 g/100 ml), but not the moderately (mean Hb = 9.2 g/100 ml) anaemic group, have a significantly (\(P<0.001\)) larger plasma volume than their controls. However, this does not give rise to an elevated blood volume but merely compensates for the lower packed cell volume of the anaemic subjects.

For a given \(\dot{V}_O_2\) the severely anaemic subjects exercise with a higher heart rate (\(P<0.001\)) than the controls; this is also true of the moderately anaemic group but the magnitude of the response is reduced (Table 2). Similarly, minute ventilation at a given \(\dot{V}_O_2\) appears slightly higher in the severely anaemic group, but larger inter-subject variability precludes these differences reaching levels of significance. For a given work load the \(\dot{V}_O_2\) is almost identical for the three groups. The mean overall mechanical efficiency for the subjects of this study is close to 23%; a value similar to that found for Europeans during work on a bicycle ergometer.
TABLE 2. The responses to exercise expressed in terms of an oxygen intake ($\dot{V}_{O_2}$) at a work load of 900 kpm/min ($\dot{V}_{O_2, 900}$), minute ventilation volume ($V_{E, 1.5}$) and cardiac frequency ($f_H, 1.5$) at a $\dot{V}_{O_2}$ of 1.5 litres/min and predicted maximum aerobic power ($\dot{V}_{O_2, \text{max.}}$) given as means ± SD.

<table>
<thead>
<tr>
<th>Group</th>
<th>$\dot{V}_{O_2, 900}$ (litres/min)</th>
<th>$V_{E, 1.5}$ (litres/min)</th>
<th>$f_H, 1.5$ (beats/min)</th>
<th>$\dot{V}_{O_2, \text{max.}}$ (litres/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>2.01 ± 0.12</td>
<td>49.4 ± 13.5</td>
<td>127 ± 9 **I,II,III</td>
<td>2.88 ± 0.46 **II</td>
</tr>
<tr>
<td>I ($n = 16$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II ($n = 7$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III ($n = 10$)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Moderately anaemic</td>
<td>2.10 ± 0.20</td>
<td>49.3 ± 6.3</td>
<td>160 ± 18 **</td>
<td>2.20 ± 0.42 **</td>
</tr>
<tr>
<td>Severely anaemic</td>
<td>2.03 ± 0.18</td>
<td>52.6 ± 10.6</td>
<td>170 ± 18 **</td>
<td>1.90 ± 0.37 **</td>
</tr>
</tbody>
</table>

** and *** values significantly different (** $P < 0.01$; *** $P < 0.001$) from the groups, shown by the roman numerals.

The higher heart rate found in the anaemic groups is accompanied by an elevated cardiac output. Thus at a given $\dot{V}_{O_2}$, stroke volume (SV) is essentially similar in the three groups (Fig. 2). The major difference in circulatory response between the groups is in the arterio-venous $O_2$ difference. For a given $\dot{V}_{O_2}$ this is lower in the anaemic groups than in their controls, the difference becoming particularly noticeable at higher levels of work (Fig. 3).

**Predicted maximum aerobic power**

The predicted maximum aerobic power ($\dot{V}_{O_2, \text{max.}}$) values are given in Table 2. In absolute
Fig. 2. Relationship of cardiac output ($\dot{Q}$) to cardiac frequency ($f_H$). The isopleths are given for stroke volumes in ml. ○, Group I (controls); ●, group II (moderately anaemic); ▲, group III (severely anaemic). --- ---, mean regression line.

Fig. 3. Relationship of oxygen uptake ($\dot{V}O_2$) to cardiac output ($\dot{Q}$). The isopleths are shown for arterio-venous $O_2$ difference in vol. %. Symbols are as in Fig. 3.
terms the mean $\dot{V}O_2_{max}$ of the severe and moderately anaemic subjects are 0.98 litre/min (~34%) and 0.68 litre/min (~24%) lower than the control group. These large differences are not removed by standardizing for body weight.

**DISCUSSION**

The results of the present study indicate that iron-deficiency anaemia causes a marked reduction in maximum aerobic power (Table 2) and increases cardiac output and plasma volume. These findings are at variance with the recent report of Cotes *et al.* (1972) but in agreement with the earlier work of Sproule *et al.* (1960). However, it must be pointed out that the conditions in the experiments of Cotes *et al.* (1972) were different from ours: they studied women working at lighter work loads and with less-marked anaemia and, as they conclude, it is dangerous to extrapolate to more severe conditions. It can be seen from Fig. 1 that during light work ($\dot{f}_H$ 110 beats/min) the $\dot{f}_H$ values overlap and there are no significant differences between the groups. It is only at the higher work loads (beyond 40% $\dot{V}O_2_{max}$) that the increase in heart rate and cardiac output appears. Although the findings of Sproule and his co-workers (1960) are in accord with the present data, this could be fortuitous. In their investigation, matched controls were not used; the comparison was between anaemic patients confined to bed and healthy young subjects. If the test subjects had not been anaemic, one would have expected large differences in maximum aerobic power between these two groups of subjects (Saltin, Blomquist, Mitchell, Johnson, Wildenthal & Chapman, 1968). Our subjects were matched for age, height, weight (see Table 1) and daily (but not recreational) habitual activity. The test subjects and the controls were work-mates from the same factory living and working under identical conditions.

An increase of plasma volume ($V_p$) at rest is in agreement with previous studies (Backman, 1961; Cropp, 1969; Duke & Abelmann, 1969), but despite the impression gained by some (Blumgart & Altschule, 1948; Cotes *et al.*, 1972), possibly from animal experiments, that severe anaemia is associated with hypovolaemia and a reduced blood volume ($V_b$) our results in man are contrary to this: $V_b$ is not significantly different between the test and control subjects. Therapy has been shown to reverse the changes in $V_p$ which accompany anaemia (Backman, 1961; Duke & Abelmann, 1969).

Our results showing an increase in cardiac output agree with the findings of others at rest (Brannon, Merrill, Warren & Stead, 1945; Starr, Collins & Wood, 1933; Roy, Bhatia, Mathur & Virmani, 1963) and during exercise (Bishop, Donald & Wade, 1955; Sproule *et al.*, 1960; Anderson & Barkve, 1970). However, in contrast to the accepted view (Liljestrand & Stenstrom, 1925; Sharpey-Schafer, 1944; Leight, Saider, Clifford & Hellems, 1951; Bishop *et al.*, 1955) at rest and during exercise, the increase of $Q$ in the present study is solely a function of $\dot{f}_H$. Stroke volume did not change with cardiac frequencies >110 beats/min (cf. Astrand, Cuddy, Saltin & Stenberg, 1964).

The difficulty in assessing the experiments cited above is that they were carried out in the supine position whereas the present studies were performed on an upright bicycle ergometer. It has been shown (Bevegård & Shepherd, 1967) that both rest and work in the supine position produces larger values of SV compared with the upright position due to a general redistribution of central blood volume and enhanced venous return. It is interesting to note that Sproule *et al.* (1960) found that although anaemic subjects had a larger SV at rest than controls the changes in exercise were only such as to make the two groups comparable. We believe that the circulatory
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system of the anaemic subject behaves in accord with Rushmore & Smith's original view for normal adults: that the major determinant of increase incardiac output is a rise in $\dot{V}O_2$, SV remaining constant, and from the present data, independent of the level of circulating haemoglobin.

Many authors have suggested that iron-deficiency anaemia may be wholly compensated for by one or several factors affecting the cardio-respiratory system: a shift to the right of the O2-dissociation curve (Rodman, Close & Purcell, 1960), a decrease in venous saturation and vascular resistance (Stead & Warren, 1947) and a reduction in blood viscosity (Richardson & Guyton, 1959). These changes may be associated with reduced diffusion capacity (Guleria, Pande, Markose, Gupta & Jain, 1971; Cotes et al., 1972), hypoxaemia and an increase in alveolar–arterial O2 gradient (Housley, 1967). Other authors have suggested from the results of animal experiments that there may be an impairment of oxidative enzymes at the tissue level in anaemia. We have no experimental evidence to confirm or refute these claims but the differences in the cardiac output data (Figs. 2 and 3) of the test subjects and controls at near maximal exercise adequately account for the predicted differences in $\dot{V}O_2$, for the two groups shown in Table 2. Further, at a $\dot{V}O_2$ of 1.5 litres/min the increase in cardiac output of 8 litres/min is sufficient to compensate for the decreased O2 capacity of the blood due to a circulating blood Hb level of approx. 6 g/100 ml. Thus although all or some of the above cited mechanisms may operate in exercise, our data would suggest that their effect is small and less important in anaemia than the compensatory tachycardia and increased cardiac output of work.

Despite this increase in cardiac rate and output, we find no support in the present study for the view of Sproule et al. (1960) that the anaerobic component of work is increased in anaemic subjects. For a given work load of 900 kpm/min, the $\dot{V}O_2$ of the test and control subjects is identical (Table 2). All the subjects in the investigation pedalled with similar mechanical efficiency independently of the level of anaemia and there were no significant differences in $\dot{V}_{1.5}$ between the groups. This latter finding is in agreement with those of Richards & Strauss (1928), Guleria et al. (1971) and Cotes et al. (1972).

The marked reduction of maximum aerobic power ($\dot{V}O_2$, max.) in anaemic subjects of 1.0 litre/min compared with control values, has important implications for the clinical and industrial medicine fields. This is particularly true for developing countries where anaemia is endemic and economic and social development depends largely on subsistence agriculture and physical labour. If iron-deficiency anaemia is left untreated it will have a serious effect on human work-output and performance. It should also be emphasized that if exercise tests are used in clinical medicine in situations where anaemia is endemic or suspected, then there is a need for standardization and care in interpreting results.

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