Hemodynamic Studies in Sickle Cell Anemia

By Leonard Leight, M.D., Thomas H. Snider, M.D., George O. Clifford, M.D., and Harper K. Hellem, M.D.

Hemodynamic studies in 13 unselected patients with sickle cell anemia are reported. Twelve of these patients were also studied during mild exercise. The cardiac output at rest was elevated in all and rose significantly with exercise in 9 of the 12 patients. The importance of the increased percentage extraction of oxygen by the tissues in modifying the response of the cardiac output is discussed. The similarity of the response to exercise in the majority of these chronically anemic patients compared with the normal response is described. Included in this series is one case with secondary cor pulmonale and one case of concurrent rheumatic heart disease.

THE clinical mimicry of rheumatic fever and rheumatic heart disease by sickle cell anemia, and the difficulty in differentiating some of the manifestations of sickle cell anemia from these conditions has been noted many times in the literature. Although rheumatic heart disease has been stated to be a rare concomitant of sickle cell disease, their occurrence together has been described. Sickle cell anemia as a cause of pulmonary vascular occlusion, pulmonary hypertension, and subsequent right ventricular hypertrophy is now well authenticated. It has been suggested that sickle cell thrombi in the coronary vasculature occasionally result in coronary insufficiency.

In view of the varied pathologic findings and the puzzling clinical picture presented by patients with sickle cell anemia, it was felt that hemodynamic studies in a group of such patients would be of interest. Furthermore, these patients offered a unique opportunity to study the circulatory adjustments to chronic and relatively constant anemia. Although studies of the circulatory state in anemia have been reported, the response of such patients to exercise has not been noted. As in other disease states affecting the cardiovascular system, knowledge of the behavior of patients during activity is essential to a more complete understanding of the circulatory state.

METHODS

All patients were studied in the fasting state, without sedation. Venous catheterization was performed in the usual fashion. When possible, a double lumen catheter was employed, the distal lumen being wedged in a branch of the pulmonary artery to obtain "pulmonary capillary" pressure. A 20-gauge needle was inserted into the brachial artery to obtain arterial blood and pressure. Cardiac output, utilizing the Fick principle, was obtained at rest, expired air for oxygen consumption being collected for three minutes in a Tissot Spirometer. Immediately upon conclusion of the determination of cardiac output, simultaneous pulmonary artery, pulmonary capillary, and brachial artery pressures were measured. The patients then exercised in the recumbent position by pedaling a bicycle at the rate of 50 to 60 revolutions per minute for three to four minutes. Simultaneous pressures in the pulmonary artery, pulmonary capillary, and brachial artery were recorded during the exercise period. Expired air for oxygen consumption was collected over the last half minute of exercise, and blood was drawn simultaneously from the pulmonary artery and brachial artery at an constant rate as possible during the entire period of air collection. Although it is recognized that a steady state may not be present under the conditions of such an exercise period, it is believed that an average cardiac output is obtained. After a period of rest, usually 10 to 15 minutes, the catheter was withdrawn and right ventricular and auricular pressures recorded.

Pressures were obtained with Sanborn Electro-manometers, and recorded on a Sanborn Polyvisio instrument. The zero point for all pressures was 10 cm. anterior to the back. Mean pressures were obtained by electrical integration. Blood samples were analyzed for oxygen content by the method of Van Slyke and Neil, duplicate samples being required to

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check within 0.1 volumes per cent. Oxygen in expired air was measured by means of a Pauling Oxygen Analyzer using a correction factor of 1.007 to convert expired volume to inspired volume.\textsuperscript{15}

The per cent oxygen utilized by the tissues expressed in terms of the arterial oxygen content was calculated as follows:

\[
\text{% oxygen utilized} = \frac{A-V \text{ oxygen difference cc./L.}}{\text{Arterial oxygen content cc./L.}} \times 100
\]

The oxygen transport to the tissues\textsuperscript{35} was expressed as follows:

\[
\text{Oxygen transport (cc./min.)} = \text{Cardiac output (L/min.)} \times \text{Arterial oxygen content (cc./L.)}
\]

Pulmonary arteriolar resistance and total peripheral resistance were expressed\textsuperscript{18} in dynes seconds cm\textsuperscript{-6}. Left ventricular work against pressure was calculated as the product of mean brachial artery pressure and cardiac output and expressed in kilogram-meters per minute.\textsuperscript{15}

**CASE MATERIAL**

Twelve patients were studied by means of cardiac catheterization both at rest and during exercise, while one patient (L.W.) was studied only during the resting state. The patients varied in age from 12 to 39 years, and had hemoglobins varying from 5.8 to 10.8 Gm. per 100 cc. (table 1). Patient J.P., who had a hemoglobin level of 10.8 Gm. per 100 cc., received 500 cc. blood the day prior to study. No other patient had received a blood transfusion for at least several weeks prior to catheterization. Cardiac hypertrophy and/or dilatation was demonstrable by means of electrocardiograms or x-ray films in all patients. Left auricular enlargement was fluoroscopically visualized in four, being of slight degree in three, and moderate degree in one. The electrocardio-

### Table 1.—Summary of Hemodynamic Findings in 13 Patients with Sickle Cell Anemia

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age</th>
<th>Hemoglobin Gm. %</th>
<th>State</th>
<th>Ventilation L/min.</th>
<th>Ox Consumption cc./min./M.\textsuperscript{2}</th>
<th>A-V O\textsubscript{2} Diff. cc./L.</th>
<th>Cardiac Output L/min.</th>
<th>Cardiac Index L./min./M.\textsuperscript{2}</th>
<th>Mean Pressures mm. Hg</th>
<th>Resistances dynes cm.\textsuperscript{5}\textsuperscript{*}</th>
<th>Work of Left Vent. Kgm./min.</th>
<th>Arterial O\textsubscript{2} Saturation %</th>
</tr>
</thead>
<tbody>
<tr>
<td>D.H.</td>
<td>12</td>
<td>9.7</td>
<td>Rest</td>
<td>7.1</td>
<td>164</td>
<td>29.3</td>
<td>6.5</td>
<td>5.4</td>
<td>75</td>
<td>28</td>
<td>-1</td>
<td>62</td>
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<tr>
<td>B.A.</td>
<td>39</td>
<td>7.7</td>
<td>Rest</td>
<td>7.8</td>
<td>178</td>
<td>28.5</td>
<td>10.2</td>
<td>6.2</td>
<td>77</td>
<td>31</td>
<td>7</td>
<td>188</td>
</tr>
<tr>
<td>J.P.</td>
<td>27</td>
<td>10.8</td>
<td>Rest</td>
<td>13.6</td>
<td>276</td>
<td>30.1</td>
<td>15.1</td>
<td>9.2</td>
<td>44</td>
<td>10</td>
<td></td>
<td>204</td>
</tr>
<tr>
<td>E.F.</td>
<td>20</td>
<td>6.0</td>
<td>Rest</td>
<td>14.0</td>
<td>291</td>
<td>31.4</td>
<td>14.7</td>
<td>8.5</td>
<td>88</td>
<td>26</td>
<td>17</td>
<td>49</td>
</tr>
<tr>
<td>P.B.</td>
<td>19</td>
<td>5.8</td>
<td>Rest</td>
<td>12.3</td>
<td>255</td>
<td>26.5</td>
<td>12.9</td>
<td>9.6</td>
<td>92</td>
<td>28</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>C.H.</td>
<td>13</td>
<td>6.7</td>
<td>Rest</td>
<td>6.3</td>
<td>160</td>
<td>28.5</td>
<td>7.1</td>
<td>5.9</td>
<td>87</td>
<td>11</td>
<td>8</td>
<td>34</td>
</tr>
<tr>
<td>S.T.</td>
<td>17</td>
<td>8.3</td>
<td>Rest</td>
<td>10.4</td>
<td>285</td>
<td>34.8</td>
<td>9.8</td>
<td>8.2</td>
<td>83</td>
<td>19</td>
<td>13</td>
<td>49</td>
</tr>
<tr>
<td>I.E.</td>
<td>37</td>
<td>8.6</td>
<td>Rest</td>
<td>10.5</td>
<td>220</td>
<td>31.5</td>
<td>13.6</td>
<td>7.0</td>
<td>98</td>
<td>19</td>
<td>10</td>
<td>53</td>
</tr>
<tr>
<td>B.G.</td>
<td>15</td>
<td>7.7</td>
<td>Rest</td>
<td>15.7</td>
<td>187</td>
<td>30.4</td>
<td>10.3</td>
<td>6.1</td>
<td>90</td>
<td>17</td>
<td>9</td>
<td>39</td>
</tr>
<tr>
<td>O.B.</td>
<td>25</td>
<td>8.4</td>
<td>Rest</td>
<td>10.1</td>
<td>197</td>
<td>31.9</td>
<td>9.7</td>
<td>6.1</td>
<td>82</td>
<td>23</td>
<td>15</td>
<td>66</td>
</tr>
<tr>
<td>L.W.</td>
<td>25</td>
<td>9.3</td>
<td>Rest</td>
<td>7.0</td>
<td>144</td>
<td>24.3</td>
<td>10.1</td>
<td>5.9</td>
<td>80</td>
<td>15</td>
<td>9</td>
<td>47</td>
</tr>
<tr>
<td>L.S.</td>
<td>19</td>
<td>7.0</td>
<td>Rest</td>
<td>7.8</td>
<td>161</td>
<td>21.5</td>
<td>10.6</td>
<td>7.5</td>
<td>80</td>
<td>15</td>
<td>10</td>
<td>38</td>
</tr>
<tr>
<td>M.S.</td>
<td>18</td>
<td>6.1</td>
<td>Rest</td>
<td>8.1</td>
<td>219</td>
<td>24.8</td>
<td>13.6</td>
<td>8.8</td>
<td>88</td>
<td>15</td>
<td>12</td>
<td>18</td>
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<tr>
<td>Averages</td>
<td>22</td>
<td>7.9</td>
<td>Rest</td>
<td>8.0</td>
<td>163</td>
<td>24.6</td>
<td>10.1</td>
<td>6.8</td>
<td>56</td>
<td>704</td>
<td>11.4</td>
<td>69</td>
</tr>
</tbody>
</table>

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graphic findings in this group of cases are shown in table 2. All patients had systolic murmurs, and three had apical diastolic murmurs. One patient (B.A.) entered the hospital in congestive failure, but was compensated at the time of study. None of the other patients had ever been in clinical cardiac failure. The subjects were unselected. Catheterization was performed as each was brought to our attention, unless there was specific contraindication or consent was not forthcoming. All fulfilled the usual laboratory and clinical criteria for sickle cell anemia, all but one having been referred from the Hematology Clinic. Electrophoretic studies* of the hemoglobin were available in seven cases, and, when obtained, indicated that those patients were suffering from true sickle cell anemia.14

**RESULTS**

The more important data obtained in the study of this group of subjects is tabulated in table 1. Cardiac index was elevated at rest in all patients, ranging from 5.1 to 15.9 liters per minute per square meter of body surface area. Patient B.G., who had a resting cardiac index of 15.9 L. per minute per square meter of surface area, was not in a basal state, since the cardiac index fell with exercise to 10.2 L. per minute per square meter accompanied by a fall in oxygen consumption from 307 to 284 cc. per minute per square meter, a decrease in ventilation from 14.4 to 9.7 L. per minute and no significant change in pulmonary pressures. Excluding this patient, the resting cardiac index ranged from 5.1 to 7.9 L. per minute per square meter, and averaged 6.1 L. per minute per square meter. All patients but one (again excluding B.G.) augmented the cardiac index with exercise (fig. 1). The exercising cardiac index ranged from 6.1 to 10.0 L. per minute per square meter and averaged 8.1 L. per minute per square meter.

The oxygen consumption at rest for the group as a whole averaged 168 cc. per minute per square meter, varying from 121 to 307 cc. Excluding patient B.G., who had a resting oxygen consumption of 307 cc. per minute per square meter, the mean resting oxygen consumption was 154 cc. per minute per square meter, and varied from 121 to 187 cc. These findings are comparable to those of Brannon and co-workers7 and Stewart and associates25 who found mean resting oxygen consumptions of 146 and 143 cc. per minute per square meter, respectively, for resting patients with less than 11 Gm. hemoglobin per 100 cc. In a group of normal subjects, Dexter and his colleagues18 found a mean resting oxygen consumption of 145 cc. per minute per square meter with a range of 127 to 168 cc.

In this series, there is no relation between the level of hemoglobin and the resting oxygen consumption. Our findings are, on the whole, in agreement with those of others who have found the basal metabolic rate to be normal or slightly elevated in anemia.22 The mean oxygen consumption during exercise was 250 cc. per minute per square meter, indicating a mild degree of work.

The arterial oxygen saturation at rest for the whole group averaged 91.7 per cent, and in 9 of 13 patients, was below 94 per cent. For the 12 exercised patients, the mean arterial oxygen saturation was 91.6 per cent. Five of

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*Electrophoretic studies were carried out by Dr. Harvey Itano, California Institute of Technology.
the 12 patients experienced a fall in arterial oxygen saturation during exercise. Among the nine individuals who had a resting saturation below 94 per cent, seven failed to raise the saturation above 94 per cent during exercise.

The work of the left ventricle against pressure exceeded 9 kilogram-meters per minute in 9 of the 13 patients at rest, averaging 11.4 kilogram-meters per minute for the whole group. In those patients in whom it was measured during exercise, the average left ventricular work rose to 15.0 kilogram-meters per minute.

Despite the presence of clinical, electrocardiographic, and/or radiologic findings compatible with organic heart disease in all of these patients, the resting pulmonary pressures were normal in all but two. One patient (B.A.), the oldest individual in this group, who had entered the hospital in congestive failure, demonstrated the hemodynamic pattern of cor pulmonale. This patient had no symptoms or signs of primary pulmonary disease. At rest, his pulmonary artery pressure was 46/22 mm. Hg with a mean pressure of 31 mm. Hg, and pulmonary capillary mean pressure of 7 mm. Hg. The corresponding mean pressures during exercise were 44 and 10 mm. Hg. The pulmonary arteriolar resistance at rest was 188 dynes second cm.⁻², showing no significant rise with exercise. At the time of catheterization, the patient was clinically free of signs of heart failure. The resting right auricular mean pressure was 1 mm. Hg. This patient appears to represent an example of cor pulmonale secondary to pulmonary vascular disease produced by sickle cell thrombi.⁴

One of the series (D.H.) demonstrated hemodynamic and clinical findings consistent with the diagnosis of concurrent sickle cell anemia and rheumatic heart disease. This individual was a 12 year old girl with a prior history of several bouts of migratory polyarthritis. She had a harsh, grade IV, apical systolic murmur and an intermittently heard rumbling apical diastolic murmur. Cardiac enlargement was demonstrated by x-ray films, left ventricular hypertrophy by electrocardiograms, and left auricular enlargement out of proportion to the generalized cardiac dilatation by fluoroscopy. At rest, the mean pulmonary capillary pressure was 23 mm. Hg, and the pulmonary artery pressure was 37/18 mm. Hg, with a mean of 28 mm. Hg. During exercise, the pulmonary artery pressure rose to 50/22 mm. Hg, with a mean of 37 mm. Hg. Pulmonary capillary pressure was not obtained during exercise. Some four months after cardiac catheterization, the patient re-entered the hospital febrile, with acute inflammatory polyarthritis, elevated sedimentation rate, and cardiac dilatation on x-ray films of a greater degree than previously noted. A subcutaneous nodule was palpable at this time on the extensor surface of her left arm immediately distal to the elbow. During her stay in the hospital, the patient experienced an episode of severe left ventricular failure. The subcutaneous nodule, which gradually regressed over a period of several days, was considered classic for rheumatic fever.

Four other patients (J.P., P.B., C.H., O.B.), who had normal resting pressures, experienced a rise in pulmonary artery pressure with exercise, the pulmonary artery pressure reaching abnormal levels in three, and increasing from a mean of 11 to 19 mm. Hg in the other patient (C.H.) (table 1). In three of these patients, this was accompanied by a slight rise in pulmonary capillary pressure, a tendency for the pulmonary artery–pulmonary capillary gradient to widen, and no significant change in pulmonary arteriolar resistance. These changes are probably related to the increased pulmonary blood flow with exercise as described in normal subjects,¹² though, in this series, there was no correlation between the increment in cardiac index incident to exercise and change in pulmonary pressures. The fourth patient (P.B.), whose mean pulmonary artery pressure rose from 17 to 28 mm. Hg with exercise, had a corresponding increase in mean pulmonary capillary pressure from 13 to 24 mm. Hg, no change in pulmonary artery–pulmonary capillary gradient, and no significant change in pulmonary arteriolar resistance. This patient had the usual sickle cell history of bouts of polyarthritis in childhood. An apical diastolic murmur and a grade I apical systolic murmur were heard on auscultation. Cardiac enlarge-
ment and prominent pulmonary artery segment were present radiographically. However, no left auricular enlargement could be demonstrated. In view of the absence of auricular enlargement, mitral stenosis seems unlikely. The increase in pulmonary pressures during exercise in this case may well have been a manifestation of high output left ventricular failure.

**Discussion**

All but one of the patients in this series had murmurs which were apparently of functional origin, such as have been previously described in sickle cell anemia and other types of anemia.1, 15, 16 Within the range of hemoglobins in this group, there did not appear to be a correlation between the degree of anemia and the intensity, type, or location of the various murmurs noted.

Cardiac catheterization disclosed complicating organic heart disease in two patients in this series. One of the patients presented the pattern of cor pulmonale which, since the pathologic studies of Yater,4 has been accepted as one of the complications of sickle cell anemia. In the absence of cardiac catheterization, this diagnosis is difficult to make, since the clinical spectrum which may be found in patients with cor pulmonale complicating sickle cell anemia may be simulated entirely by the anemia, per se.

In the other case, the hemodynamic findings, coupled with the clinical findings, were indicative of mitral valvulitis. The incidence of rheumatic fever among patients with sickle cell anemia remains a subject of considerable controversy. As a result of the studies of Klinefelter1 and others, the difficulties in clinically separating the signs and symptoms of rheumatic fever and sickle cell anemia have become widely recognized. However, such a separation is of importance in view of the therapy available for the treatment of the acute attack of rheumatic fever, and the demonstrated usefulness of prophylactic medication in preventing future attacks and some of the complications of this disease. The case here described emphasizes this point. Despite the findings of mitral valvular disease, there was reluctance to start this patient on indefinite prophylactic penicillin therapy because of the many reports indicating the infrequent concurrence of rheumatic heart disease and sickle cell anemia. The subsequent episode of acute rheumatic fever some months later might have been prevented if such prophylactic therapy had been instituted.

Porter17 has recently suggested, on the basis of his experience with patients suffering from chronic parasitic anemia, that the cardiac output is not increased at rest in the patient with chronic, severe, and constant anemia. Our findings are not in accord with this viewpoint. The mean resting cardiac index of 6.1 L. per minute per square meter of body surface area in this group is significantly higher than the mean normal values of 3.32 to 4.2 L. per minute per square meter reported by various authors using the same technic.12, 18-20 Our results in sickle cell anemia are comparable to those of Brannon and associates,7 who reported a mean cardiac index of 5.7 L. per minute per square meter in a variety of anemic patients with hemoglobins of less than 10 Gm. per 100 cc.

Although the cardiac index was elevated at rest in all patients, the level of cardiac index bore no relation to the hemoglobin or oxygen content levels. This lack of a linear relationship between the cardiac index and the oxygen content appears to be explained by a peripheral compensatory mechanism whereby the percentage of oxygen extraction is increased as the oxygen content of the arterial blood decreases. Excluding patient B.G., the mean arteriovenous oxygen difference at rest was 25.1 cc. per liter, and the mean utilization of oxygen expressed as per cent of arterial oxygen content was 26.8 per cent (table 3). The tendency for the per cent of oxygen extracted from the arterial blood to increase as the oxygen content decreases is illustrated in figure 2 and is in agreement with the findings of Liljestrand.21 This relationship is better demonstrated in figure 3, where the oxygen transport to the tissues is related to the percentage extraction of oxygen. It is apparent that as the quantity of oxygen delivered to the tissues per minute decreases, the percentage
TABLE 3.—Data Relating Oxygen Content, Oxygen Transport, and Oxygen Utilization

<table>
<thead>
<tr>
<th>Patient</th>
<th>O₂ Content cc./L.</th>
<th>A-V O₂ Difference cc./L.</th>
<th>Cardiac Output L./min.</th>
<th>O₂ Transport cc./min.</th>
<th>O₂ Utilization in % of O₂ Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>D. H.</td>
<td>125.5</td>
<td>125.1</td>
<td>29.3</td>
<td>38.4</td>
<td>6.5</td>
</tr>
<tr>
<td>B. A.</td>
<td>90.4</td>
<td>90.8</td>
<td>28.5</td>
<td>30.1</td>
<td>10.2</td>
</tr>
<tr>
<td>J. P.</td>
<td>124.8</td>
<td>125.5</td>
<td>27.3</td>
<td>34.1</td>
<td>9.3</td>
</tr>
<tr>
<td>E. F.</td>
<td>71.2</td>
<td>66.7</td>
<td>19.2</td>
<td>23.3</td>
<td>8.9</td>
</tr>
<tr>
<td>P. B.</td>
<td>68.6</td>
<td>65.6</td>
<td>26.5</td>
<td>26.5</td>
<td>6.9</td>
</tr>
<tr>
<td>C. H.</td>
<td>80.7</td>
<td>84.8</td>
<td>28.5</td>
<td>34.8</td>
<td>7.1</td>
</tr>
<tr>
<td>S. T.</td>
<td>107.3</td>
<td>109.8</td>
<td>21.0</td>
<td>31.5</td>
<td>14.5</td>
</tr>
<tr>
<td>I. E.</td>
<td>107.6</td>
<td>108.7</td>
<td>30.4</td>
<td>41.5</td>
<td>10.3</td>
</tr>
<tr>
<td>O. B.</td>
<td>103.3</td>
<td>104.0</td>
<td>22.1</td>
<td>31.9</td>
<td>9.2</td>
</tr>
<tr>
<td>L. W.</td>
<td>116.6</td>
<td></td>
<td>24.3</td>
<td></td>
<td>10.1</td>
</tr>
<tr>
<td>L. S.</td>
<td>83.1</td>
<td>82.3</td>
<td>21.5</td>
<td>26.9</td>
<td>10.6</td>
</tr>
<tr>
<td>M. S.</td>
<td>76.5</td>
<td>75.5</td>
<td>22.1</td>
<td>24.8</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Mean .................... 25.1  31.3  26.8  33.6

The extraction of oxygen from the arterial blood increases. This important compensatory phenomenon is probably due to an increased capillary diffusing surface in such patients\textsuperscript{21, 24} and serves partially to satisfy the needs of the tissues for sufficient oxygen in face of a lowered oxygen carrying capacity of the blood.

Despite the fact that with increasing anemia there is a tendency to extract a greater percentage of available oxygen at the periphery, this mechanism fell far short of providing the needs of the tissues for oxygen in this group. The absolute quantity of oxygen delivered to the periphery in terms of the arteriovenous difference was less than in normal subjects, and the per cent utilization in terms of oxygen content less than is seen in other conditions at rest, for example, in patients with congestive failure.

As previously noted (fig. 1), all but two patients responded to exercise with an increase in cardiac index. Of the two patients who had a fall in cardiac index with exercise, one of them, patient B.G., a 15 year old boy with a hemoglobin of 7.7 Gm. per 100 cc., has been mentioned previously as not being in a basal state at rest. Nevertheless, his resting cardiac index of 15.9 L. per minute per square meter of body surface area illustrates his capacity for increasing his cardiac output to high levels. We have no explanation for the failure of the other patient (S.T.) to increase his cardiac output with exercise. Since there was no significant change in pulmonary pressures with exercise, it is not believed that this was due to cardiac failure. Patient (P.B.), who increased his cardiac index with exercise, probably suffered mild left ventricular failure during the exercise period.

The response of normal individuals to exercise shows considerable variation. According to Ferrer and associates\textsuperscript{9} the normal individual, when exercised, will increase his cardiac output by 600 cc. or more per 100 cc. increase in oxygen consumption. Similar data have been calculated for the entire

![Fig. 2. Relation between arterial oxygen content and oxygen utilized by tissues, expressed as per cent of arterial oxygen content.](http://circ.ahajournals.org/)

**Fig. 2.** Relation between arterial oxygen content and oxygen utilized by tissues, expressed as per cent of arterial oxygen content.
group and are illustrated in Table 4. Of the patients who increased their cardiac output with exercise, all but one increased it by more than 600 cc. per 100 cc. increase in oxygen consumption. This includes the two individuals who are believed to have organic disease. Although the capacity to respond to exercise is, in general, restricted in patients with mitral stenosis, we have not infrequently seen a normal response to exercise of this degree in patients with mild to moderate mitral stenosis. Patients with mild cor pulmonale due to emphysema frequently have a normal response to exercise.20

That the response of the cardiac output to bodily needs was essentially normal is well illustrated by the results obtained with exercise. For the group, excepting patient B.G., the mean arteriovenous oxygen difference during exercise rose to 31.3 cc. per liter and the mean per cent oxygen utilization in terms of the oxygen content rose to 33.6 per cent (Table 3). Using the data of Hickam20 obtained in a group of normal individuals, the calculated mean per cent oxygen utilization in terms of oxygen content during exercise was 31.8 per cent. The essential similarity between the two figures is further evidence for the normal response among this group of patients. The percentage utilization among these patients with sickle cell anemia is far below that which may occur among patients with little cardiac reserve who are exercised and who can meet conditions of stress only by increasing the peripheral utilization of oxygen.

The work of the left ventricle in the majority of these patients was elevated at rest. This is in disagreement with the findings of Stewart and coworkers26 who studied a group of patients suffering from pernicious anemia. Since, in the range of 7 to 9 Gm. hemoglobin per 100 cc., the coronary blood flow is said to be normal or low and the oxygen consumption of the myocardium per unit weight low,26 the efficiency of the heart among many of these patients must have been high. The fact that these patients were able to maintain an abnormally high level of cardiac work and efficiency for an indefinite period of time gives eloquent testimony concerning the reserve inherent in the human heart. At lower levels of hemoglobin, there is evidence that the coronary blood flow is high.26 This is probably an important factor in maintaining cardiac reserve among anemic patients whose arterial oxygen content is so low that insufficient oxygen is available for extraction by the myocardium.

Whether the low resting arterial oxygen saturation observed in the majority of these patients is unique in sickle cell anemia is not clear. Other instances of the recording of low arterial oxygen saturation in sickle cell anemia have been found.1,29-31 The oxygen dissociation curve of sickle cell hemoglobin is reported to

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**Table 4.—Changes in Cardiac Output and Oxygen Consumption with Exercise**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Change in O₂ Consump. with Exercise cc./min.</th>
<th>Change in Cardiac Output with Exercise cc./min.</th>
<th>Change in Card. Output per 100 cc. Change in O₂ Consumption</th>
</tr>
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<td>D.H.</td>
<td>+95</td>
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<td>−900</td>
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<td>+2000</td>
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<td>B.G.</td>
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<td>M.S.</td>
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<td>+5100</td>
<td>+3400</td>
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**Fig. 3.** Relation between oxygen transport to tissues and oxygen utilized, expressed as per cent of arterial oxygen content.
be normal. Although the oxygen saturation in anemia is said to be normal, Rasmussen found the arterial oxygen saturation low in 6 of 12 resting patients with various types of anemia. Ryan has presented evidence that the alveolar-arterial gradient in anemia is significantly increased and the oxygen tension of arterial blood decreased. Further studies to elucidate this point are contemplated.

The failure of the oxygen saturation to rise during exercise in some of these patients is in accordance with the findings of Himwich, who found that the exercising oxygen saturation was lower than the resting saturation in five patients with anemia. This is probably due to increased venous admixture during exercise.

**Summary**

1. Hemodynamic studies during the resting state have been carried out in 13 unselected patients with sickle cell anemia. Twelve patients were also studied during mild exercise.

2. The cardiac index at rest for the 12 patients considered to be in a basal state averaged 6.1 L per minute per square meter of body surface area. The mean cardiac index during exercise rose to 8.1 L per minute per square meter.

3. There was no demonstrable relationship between the resting cardiac output and the oxygen content or hemoglobin level. The percentage oxygen extraction by the peripheral tissues tended to vary inversely with the arterial oxygen content and the oxygen transported to the tissues per minute.

4. Nine of the 12 patients had a normal increase in cardiac output during exercise. One patient had an unexplained slight fall in cardiac output during exercise, and one a less than expected increase in output. One patient, who had a fall in cardiac output during exercise, was not in a basal state at rest. One patient, who increased his cardiac output during exercise, exhibited left heart failure during the exercise period.

5. Despite cardiomegaly and murmurs in all patients, cardiac catheterization failed to reveal any abnormality other than high cardiac output in all but two. One patient presented the hemodynamic pattern of cor pulmonale.

Another of the series is presented as an example of concurrent organic mitral valvular disease and sickle cell anemia on the basis of hemodynamic and clinical data.

6. The mean resting arterial oxygen saturation was 91.7 per cent and was below normal in 9 of the 13 patients. The mean oxygen saturation during exercise was 91.6 per cent, 5 of the 12 patients experiencing a fall in saturation during exercise.

**Sumario Español**

1. Estudios hemodinámicos durante el descanso han sido llevados a cabo en 13 pacientes no seleccionados con anemia de hematóides falciformes. Doce pacientes también fueron estudiados durante el ejercicio moderado.

2. El índice cardíaco durante el descanso en los 12 pacientes considerados estar en condiciones basales fue 6.1 L por minuto por metro cuadrado de superficie de cuerpo. El índice promedio durante el ejercicio aumento a 8.1 L por minuto por metro cuadrado.

3. No hubo relación demostrable entre la producción cardíaca durante el descanso y el contenido de oxígeno o nivel de hemoglobina. El porcentaje de extracción de oxígeno por los tejidos periféricos tendió a variar inversamente con el contenido arterial de oxígeno y el oxígeno transportado a los tejidos por minuto.

4. Nueve de los 12 pacientes tuvieron un incremento normal en producción cardíaca durante el ejercicio. Un paciente tuvo un ligero no explicado decremento en producción cardíaca durante el ejercicio, y uno un aumento menos de lo esperado en producción cardíaca. Un paciente, que tuvo decremento en producción cardíaca durante el ejercicio, no estuvo en condiciones basales durante el descanso. Un paciente, que aumento su producción cardíaca durante el ejercicio, mostró descompensación del corazón izquierdo durante el período de ejercicio.

5. No obstante engrandecimiento cardíaco y soplos en todos los pacientes, el cateterismo cardíaco no reveló ninguna anormalidad otra que una producción cardíaca alta en todos excepto dos casos. Un paciente presentó el
patrón hemodinámico de cor pulmonale. Otro de la serie se presenta como un ejemplo de enfermedad orgánica mitral valvular concurrente con anemia de hematías falciformes a base de hemodinámica y datos clínicos.

6. El promedio de saturación arterial de oxígeno durante el descanso fue 91.7 por ciento y fue por debajo de lo normal en 9 de 13 pacientes. El promedio de saturación de oxígeno durante el ejercicio fue 91.6 por ciento, 5 de los 12 pacientes experimentaron una caída en saturación durante el ejercicio.

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