Cardiac Enlargement in Chronic Severe Anemia

By L. M. Sanghvi, M.R.C.P. (Lond.), D.T.M.&H. (Eng.),
S. N. Misra, M.D., and K. Banerjee, M.D.

Although cardiac enlargement in patients with chronic severe anemia was reported earlier in necropsy studies,\textsuperscript{1, 2} it was first demonstrated roentgenologically by Ball,\textsuperscript{3} who also showed that enlargement disappeared with correction of anemia. Enlargement has been attributed to dilatation or hypertrophy associated with dilatation.\textsuperscript{4-7} Experimentally Ludke and Schuller\textsuperscript{8} demonstrated cardiac dilatation in dogs after producing anemia. Cardiac hypertrophy also has been described in experimentally produced anemia.\textsuperscript{9-12} Paplanus et al.,\textsuperscript{12} in a recent study in which severe anemia was produced in dogs by repeated venesections, demonstrated that anemia per se can cause cardiac hypertrophy. The mechanism of cardiac enlargement and its relationship to hemoglobin level and other factors are uncertain. In this country severe curable anemias associated with a high incidence of cardiac enlargement and of complicating congestive failure are frequently encountered. It was thought therefore that study of a large series of patients until the anemia was cured may prove of value in assessing the nature of cardiac enlargement and its relation to various factors. The purpose of this communication is to report the results of such a study in 150 patients.

Material and Methods

One hundred and fifty patients with anemia of at least 3 months' duration and hemoglobin levels of less than 8 Gm. per 100 ml. were studied. Only patients who were hospitalized until the anemia was cured and in whom no evidence of any other cardiovascular disease could be detected after cure of anemia were included in the study. There were 93 male and 57 female patients, with ages varying from 10 to 55 years (table 1). The hemoglobin level varied from 1 to 8 Gm., with an average of 3.5 Gm. Anemia was due to chronic malaria in 80 cases, ankylostomiasis in 32, chronic dysentery in 11, bleeding hemorrhoids in 8, and uterine bleeding in 8, and was of undetermined etiology in 11 cases. Duration of anemia varied from 3 months to 5 years, with an average of 13 months. Congestive cardiac failure was considered to be present in 43 patients, of whom 24 were female.

Fluoroscopic examination of the heart chambers, direct measurement of the venous pressure, and estimation of circulation time by magnesium sulfate method were done on admission. Chest roentgenograms were taken usually twice, on admission and after cure of anemia. The heart was considered enlarged if the cardiothoracic ratio was more than 50 per cent. Duration of anemia was difficult to ascertain accurately. For the purpose of this study the first appearance of symptoms, such as weakness and fatigability, exertional dyspnea, palpitation, and anorexia, was considered; the actual duration of anemia was probably much longer than estimated. Heart failure was diagnosed after careful evaluation of edema, hepatomegaly, orthopnea, venous pressure, circulation time, and rapidity of regression of hepatic and cardiac enlargement, because many of these manifestations may be present without failure. Patients were divided into 3 arbitrary groups according to hemoglobin levels; less than 3 Gm., 3 to 5 Gm., and more than 5 Gm. per 100 ml. Statistical evaluation of the data was done by the chi-square test.

Apart from treatment of the etiologic factor, routine therapy included administration of saccharated oxide of iron intravenously and ferrous sulfate and multivitamin pills orally. Because of the difficulty of obtaining donors, blood transfusion was given initially mostly to patients with hemoglobin of less than 3 Gm. per 100 ml. or with heart failure.

Results

Enlargement of the cardiac shadow was found in 120 patients, including all the 43 patients with cardiac failure; the cardiothoracic ratio in these patients varied from 51 to 82 per cent, with an average of 55 per cent.

The relation of the cardiothoracic ratio to the hemoglobin level and heart failure is given in table 2. The relation of failure, enlargement, and cardiothoracic ratio of more than 55 per cent to hemoglobin level and sex is given in table 3. A highly significant difference was found in the incidence of cardiac...
Table 1

Age and Sex Distribution

<table>
<thead>
<tr>
<th>Age (yr.)</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-20</td>
<td>39</td>
<td>15</td>
<td>54</td>
</tr>
<tr>
<td>21-30</td>
<td>31</td>
<td>25</td>
<td>56</td>
</tr>
<tr>
<td>31-40</td>
<td>9</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>41-50</td>
<td>13</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>51-55</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>57</td>
<td>150</td>
</tr>
</tbody>
</table>

Table 2

Relation of Cardiotoracic Ratio to Hemoglobin Level and Failure on Admission

<table>
<thead>
<tr>
<th>Hgb. Gm./%</th>
<th>Total cases</th>
<th>No. with Cardiotoracic ratio %</th>
<th>Mean Cardiotoracic ratio %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>up to 55</td>
<td>55-65</td>
</tr>
<tr>
<td>&lt;3</td>
<td>61</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>3-5</td>
<td>66</td>
<td>48</td>
<td>15</td>
</tr>
<tr>
<td>&gt;5</td>
<td>23</td>
<td>22</td>
<td>1</td>
</tr>
</tbody>
</table>

Without failure 107 90 16 1 0 50 ± 5.7
With failure 43 10 20 9 4 62 ± 8
Total 150 100 36 10 4 55 ± 8

failure ($\chi^2 = 21.11; p<.001$) as well as in the number of patients with a cardiotoracic ratio of more than 55 per cent ($\chi^2 = 18.06; p<.001$) in the 3 hemoglobin groups, but no significant difference was found in the incidence of enlargement. Of the 23 patients with more than 5 Gm. of hemoglobin, none had heart failure and only 1 had a cardiotoracic ratio of more than 55 per cent. Of 107 patients without failure, 90 had a cardiotoracic ratio up to 55 per cent and only 1 had more than 65 per cent. A cardiotoracic ratio up to 55 per cent was, however, seen in 10 patients with failure and in 31 patients with less than 3 Gm. of hemoglobin.

The incidence of enlargement was nearly equal in male and female patients. Incidence of heart failure was, however, significantly greater in women ($\chi^2 = 8.02; .003<p<.005$). This appeared to be largely responsible for the greater degree of cardiac enlargement in women. The average cardiotoracic ratios among cases with enlarged heart were 59 and 55 per cent for female and male patients, respectively. Cardiotoracic ratios of more than 55 and 65 per cent, respectively, were found in 29 (51 per cent) and 10 (17 per cent) women and 21 (22 per cent) and 4 (4 per cent) men.

The age of the patient and the etiologic factor or the duration of anemia (table 4) were

Figure 1

Roentgenograms of a 35-year-old woman with cardiac failure. Top. Typical mitral valve configuration (cardiotoracic ratio 70 per cent). Bottom. Slight cardiac enlargement (cardiotoracic ratio 52 per cent) after cure of anemia.
not found to have any significant relation to the incidence of cardiac enlargement and failure.

The type of cardiac enlargement was generalized in 43 cases, predominantly left ventricular in 31, predominantly right ventricular with prominent conus or pulmonary artery

Table 3
Relation of Cardiac Failure and Enlargement to Hemoglobin Level and Sex

<table>
<thead>
<tr>
<th>Hgb. Gm./%</th>
<th>Total cases</th>
<th>No. with failure</th>
<th>No. with enlargement</th>
<th>Cardiothoracic ratio ≥55%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>61</td>
<td>29 (48%)</td>
<td>54 (88%)</td>
<td>31 (50%)</td>
</tr>
<tr>
<td>3.5</td>
<td>66</td>
<td>14 (21%)</td>
<td>50 (75%)</td>
<td>18 (27%)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>23</td>
<td>—</td>
<td>16 (70%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

Sex
- M: 93 cases, 19 (20%), 73 (78%), 21 (22%)
- F: 57 cases, 24 (42%), 47 (82%), 29 (51%)

Table 4
Relation of Cardiac Failure and Enlargement to Duration of Anemia

<table>
<thead>
<tr>
<th>Duration (yr.)</th>
<th>Total cases</th>
<th>Per cent failure</th>
<th>Per cent enlargement</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>95</td>
<td>23</td>
<td>75</td>
</tr>
<tr>
<td>1-3</td>
<td>42</td>
<td>40</td>
<td>88</td>
</tr>
<tr>
<td>&gt;3</td>
<td>13</td>
<td>30</td>
<td>92</td>
</tr>
</tbody>
</table>

(fig. 1) in 43, and pear-shaped (figs. 2 and 3) in 3 cases. The present series confirmed the previous observation in a smaller series that right and left ventricular types of enlargement were usually seen in cases with and without tachycardia, respectively. In 2 cases with pear-shaped cardiac silhouette, on paracentesis, 100 and 150 ml., respectively, of clear straw-colored fluid were aspirated from the pericardial sac; the enlarged silhouette was chiefly due to cardiac enlargement and only to a small extent to pericardial effusion. Both cases had congestive failure. In another case paramediastinal effusion on the right side simulated marked dilatation of the right atrium.

Cardiac size decreased rapidly with correction of anemia and relief of heart failure; it returned to normal (fig. 4) in 92 of the 120 cases with enlargement on admission. Some enlargement, however, persisted after cure of the anemia in 28 cases (figs. 1 to 3). The cardiothoracic ratio after cure in these cases ranged between 52 and 58 per cent, with an average of 54 per cent. Significant difference was found in the incidence of persistent enlargement (table 5) in cases with and without failure ($\chi^2 = 11.93; p<.001$) and

Figure 2
Roentgenograms of a 45-year-old man with cardiac failure and pericardial effusion. Top. Pear-shaped cardiac shadow (cardiotoracic ratio 68 per cent). Bottom. Persistent enlargement (cardiotoracic ratio 54 per cent) 14 weeks later and 5 weeks after cure of anemia.
Table 5
Relation of Persistent Enlargement to Hemoglobin Level and Failure

<table>
<thead>
<tr>
<th>Hgb. Gm./%</th>
<th>Enlargement</th>
<th>Total cases</th>
<th>Per cent persistence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td></td>
<td>54</td>
<td>35</td>
</tr>
<tr>
<td>3.5</td>
<td></td>
<td>50</td>
<td>14</td>
</tr>
<tr>
<td>&gt;5</td>
<td></td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Without failure</td>
<td></td>
<td>77</td>
<td>13</td>
</tr>
<tr>
<td>With failure</td>
<td></td>
<td>43</td>
<td>42</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>120</td>
<td>23</td>
</tr>
</tbody>
</table>

in the 3 hemoglobin groups ($\chi^2 = 7.13; p<0.018 <p<0.030$), particularly in those with less than 3 Gm. and more than 3 Gm. ($\chi^2 = 7.42; p<0.005 <p<0.008$). The cardiothoracic ratio on admission was more than 60 per cent in 25 and more than 55 per cent in 27 of the 28 cases, and 18 of them had heart failure.

Discussion
The high incidence of cardiac enlargement in the present series is apparently due to the greater intensity of anemia in our patients. Within the scope of this study the actual incidence of enlargement was not found to have significant relation to age and sex of the patient, the duration or the etiologic factor of anemia and the hemoglobin level. This suggests that enlargement is very likely to occur when the hemoglobin level falls below 8 Gm. per cent and that it is due to the anemia per se. There was no consistent relation between the cardiac size and the hemoglobin level on admission. Evaluation of the data, however, revealed a significant difference in the cardiothoracic ratio and incidence of cardiac failure at various hemoglobin levels. Cardiac failure as well as considerable enlargement was seen only in cases with hemoglobin values of 5 Gm. or less, and the latter was mostly associated with failure. In two other series of heart failure due to anemia the hemoglobin was less than 5 Gm. in all the cases.

An interesting feature was a significantly larger cardiac size and increased incidence of cardiac failure in female than in male patients, while there was no significant difference in the incidence of enlargement. It has been commented upon that exertion during the anemic state plays an important role in the production of cardiac enlargement and causation of failure. In our series women

Figure 3
Roentgenograms of a 17-year-old girl with cardiac failure. Top. Considerable cardiac enlargement (cardiothoracic ratio 82 per cent). Bottom. Persistent enlargement (cardiothoracic ratio 58 per cent) 15 weeks later and 6 weeks after cure of anemia.
were mostly housewives doing light manual work while men were mostly laborers or cultivators doing heavy manual work. It is conceivable that men, because of their heavy work as wage earners, notice symptoms and seek treatment earlier. Their heart size even when heart failure develops would therefore be comparatively less than women, who usually seek treatment only when they are incapacitated because of the severity of anemia or heart failure. This view is supported by the finding that of the 10 patients with failure and a cardiothoracic ratio of less than 55 per cent, 8 were men.

With correction of anemia the heart size diminished rapidly; it returned to normal in 77 per cent of the cases with initial enlargement. Enlargement in these cases can therefore be attributed to dilatation alone. The maximum cardiothoracic ratio among these cases was as high as 70 per cent (fig. 4), showing the extent to which the heart can dilate and yet return to a normal size. This return occurred usually when the hemoglobin level rose to more than 12 Gm. per 100 ml. and within a period of 4 to 10 weeks.

In 23 per cent of the cases, the heart remained enlarged despite cure of the anemia. The maximum cardiothoracic ratio after cure in these cases was 58 per cent, showing that cardiac enlargement above this size in all our cases was due to dilatation. It is realized that in some of the cases the heart size may still return to normal in the course of time. Use of the cardiothoracic ratio as an index of enlargement is only a rough guide and may sometimes be inaccurate, since the relationship between the diameter of the heart and that of the chest varies considerably. In a control series of normal individuals in Jaipur the cardiothoracic ratio ranged between 39 and 47 per cent, with an average of 44 per cent. A cardiothoracic ratio of more than 50 per cent in our cases is therefore considered to represent definite cardiac enlargement. Instances of persistent enlargement have been reported previously. The high incidence in the present series is probably due to the greater intensity of anemia and high incidence of heart failure. Enlargement was persistent irrespective of the age of the patient (fig. 3), and there was little possibility of associated coronary artery disease being responsible for it. The possibility of vitamin or nutritional deficiency as a cause is unlikely because all the patients were given a mul-

**Figure 4**

*Roentgenograms of a 25-year-old man with cardiac failure. Top. Considerable cardiac enlargement (cardiothoracic ratio 70 per cent). Bottom. Normal size heart (cardiothoracic ratio 45 per cent) 8 weeks later.*
CARDIAC ENLARGEMENT IN ANEMIA

tivitamin pill including vitamin B-complex factors and a high-protein diet during the period of hospitalization.

Electrocardiographic and ballistocardiographic abnormalities have been reported to persist in some cases after cure of anemia, and the possibility that some dilatation may persist if the cardiac damage has been severe, with persistence of mechanical inefficiency, cannot be ruled out. It has, however, already been seen that even a markedly enlarged heart returns rapidly to normal size with cure of anemia, thus demonstrating that enlargement due to dilatation alone disappears completely. Persistent enlargement was mostly seen in cases with large hearts on admission. Furthermore, cardiac hypertrophy has been noted at necropsy in patients with anemia as well as in experimentally produced anemia. It is therefore most likely that persistent enlargement is associated with hypertrophy although this may be accompanied by some dilatation.

The presence of pericardial effusion in patients with congestive failure due to anemia has not so far been demonstrated during life in any case. In the present series effusion was demonstrated in 2 cases, both of whom recovered completely from anemia. At necropsy serous pericardial effusion in patients who died of congestive failure apparently due to pernicious anemia, and lemon-yellow hydropericardium in cases of erythroblastic anemia have been noted. Soloff and Bello drew attention to the difficulty in differentiating roentgenographically cardiac dilatation from pericardial effusion in patients with anemia and were the first to demonstrate effusion during life in 2 patients with anemia. The heart was normal in size in both patients, and the effusion was not due to congestive failure. It may have been due to hemopigmentary pericarditis or to redistribution of fluid within the functional body compartments. Both of our cases had definite congestive failure and large hearts, and the effusion was apparently due to heart failure and not due to anemia. Some enlargement of the heart persisted after cure of anemia in both cases.

Summary

One hundred and fifty patients with chronic severe anemia were studied to determine the nature of cardiac enlargement and its relation to various factors.

Enlargement was present in 120 patients. It showed no consistent relation to the hemoglobin level on admission. A significant increase in the cardiac size and incidence of failure was observed with increased severity of anemia, and in female as compared to male patients. The incidence of enlargement showed no relation to the age and sex of the patient and the duration or the etiologic factor of anemia.

With correction of the anemia, enlargement disappeared rapidly in 92 patients, indicating that it was due to dilatation alone. Some enlargement persisted in 28 patients, and it is believed to be associated with cardiac hypertrophy.

Pericardial effusion due to heart failure in 2 patients contributed to a small extent to the enlargement of the cardiac shadow.

Acknowledgment

Our thanks are due to Dr. L. R. Sarin, Superintendent, Sawai Man Singh Hospital, for permission to publish this report, and to Dr. R. Sharma for statistical evaluation of the data.

Summario in Interlingua

Cento cinquanta patientes con formas sever de anemia chronic eseva studiate pro determinar la natura del allargamento cardiaque in illes e su relation con varie factores.

Allargamento cardiaque eseva presente in 120 del casus. Illo mostrava nulle uniforme relation con le nivello de hemoglobina al tempore del hospitalisation. Un significative augmento del dimensiones cardiaque e del incidentia de disfallimento eseva observate con le augmento del grado de severitate del anemia e in femininas in comparation con masculos. Le incidentia del allargamento cardiaque mostrava nulle relation al etate e al sexo del patientes e al duration o al factores etiologic del anemia.

Con le correction del anemia, le allargamento cardiaque disparea rapidemente in 92 patientes. Isto indicava que le condition eseva causate exclusive mente per un dilatation del corde. Un certe grado de allargamento cardiaque persisteva in 28 patientes. Es opinate que isto eseva associate con hypertrophia cardiaque.

Effusion pericardiale causate per disfallimento card-
References

Quite characteristic of the habit of the human mind, we seem to find considerable comfort in interpreting an experience if we can find a plausible or even generally accepted cause for it. If we think we know its cause, in some measure we are at least relieved. Likewise, we take similar solace from giving it a name even when thinking about the name might raise more questions than it answers.—Alan Gregg, M.D. Challenges to Contemporary Medicine. New York, Columbia University Press, 1956, p. 20.
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