Chronic Hemolysis following Fascia Lata and Starr-Edwards Aortic Valve Replacement


SUMMARY
Sixty-two patients were investigated for chronic intravascular hemolysis from 3 months to 6\% years following aortic valve replacement; 27 patients had Starr-Edwards prostheses and 35 fascia lata grafts. The findings are suggestive of a significantly higher incidence and degree of hemolysis in patients with Starr-Edwards prostheses compared to those with fascia lata grafts. In both groups regurgitation was an important factor in producing hemolysis. In the absence of regurgitation fascia lata grafts do not produce significant hemolysis, while Starr-Edwards valves traumatize the red cells even in the absence of regurgitation. Starr-Edwards valves of small size are associated with hemolysis more often than larger ones are. Turbulent flow due to the obstructing ball is the probable mechanism of hemolysis in these patients. In most of the patients the degree of hemolysis appears to remain at the same level of activity. In rare instances, however, the hemolysis may regress. The mechanism for this is not clear. In a small number of patients, also, progressive hemolysis may necessitate removal and replacement of the valve.

Additional Indexing Words:
Biologic tissue valves
Lactic dehydrogenase
Hemolytic anemia
Red cell fragmentation
Haptoglobins
Regurgitant valves

CHRONIC intravascular hemolysis following the replacement of diseased heart valves by prosthetic devices has been previously reported.\textsuperscript{1-8} In a few cases uncontrolled hemolytic anemia has necessitated removal of the prosthesis and replacement by another valve.\textsuperscript{3, 5}

There are only a few reports concerned with hemolysis following homograft\textsuperscript{9} and heterograft\textsuperscript{7, 10} valve replacements, and none following fascia lata grafts.

In recent years fascia lata grafts have been used to replace heart valves.\textsuperscript{11-14} The present work was undertaken to study the incidence of hemolysis and the factors involved in its production in patients with aortic valve replacement with mounted fascia lata grafts as compared to similar studies following the use of prostheses.

Methods
Data were obtained from 62 patients with aortic valve replacement, who agreed to participate in this study. Twenty-seven patients had Starr-Edwards prostheses (group I), and 35 had frame-mounted fascia lata grafts (group II). Two patients in group II had had concomitant mitral valve surgery; one of them had open mitral valvotomy and the other mitral valve repair. This study was carried out 2\% to 6\% years following operation on group I and 3 months to 2\% years postoperatively on group II. A minimum interval of 3 months between the operation and the time of study was decided upon to avoid the effect of immediate postoperative changes in red cell
survival due to operative trauma and blood transfusion. The age distribution of the patients in both groups was essentially similar and ranged from 18 to 63 years, the average being 47.3 years in group I and 46.6 years in group II.

In group I, 15 patients had small Starr-Edwards prostheses (no. 8, 9, or 10) while 12 had "large" prostheses (no. 11 or 12). Twenty-one had the silastic ball type while six had the composite seat prosthesis.

In group II, 14 patients had small fascial grafts (internal diameter, 18 or 20 mm) and 21 had large grafts (internal diameter, 22 or 24 mm). Twelve had fresh autologous and 23 had preserved homologous fascia lata grafts.

Six patients in group I and seven in group II had aortic diastolic murmurs and were considered to have aortic regurgitation. This, however, does not reflect the true incidence of aortic incompetence in a larger number of patients operated upon. Patients with aortic diastolic murmurs were particularly asked to participate in this study. Detailed clinical and hemodynamic results are being reported separately. In each group data on the patients with and without regurgitation have been compared.

The presence and the degree of hemolysis were evaluated from the laboratory studies performed without the knowledge of the identity or clinical status of the patient. Hemoglobin and hematocrit were determined on a Coulter counter (model S); reticulocyte count, Coombs' test, and detection of urinary hemosiderin were performed according to the methods of Dacie and Lewis. The enumeration of red cell fragments was performed on a well-spread film stained with May-Grünwald-Giemsa’s stain, and the statistical basis of the count was similar to that of the reticulocyte count. Haptoglobin electrophoresis was carried out on the Gelman Sepra tek system with tris-EDTA-borate buffer pH 9.1. Total serum bilirubin was determined on an autoanalyzer by the method of Simmons and plasma lactic dehydrogenase by the method of Wootton. Serum iron level was measured by a modification of the method of Young and Hicks. The normal values for these parameters in this laboratory are given in table 1.

Results

Clinical Findings

Six patients in group I (with prostheses) had had clinical evidence of hemolysis in the past and had required treatment with iron and blood transfusions. Since this study was completed, two of these patients have required removal and replacement of their prostheses due to intractable chronic hemolysis. One of them had a perivalvular leak, and in the other the clot covering of the struts of the prosthesis was fragmented and contained fibrinous deposits. None of the patients in group II (with fascial grafts) had sufficient evidence of chronic hemolysis to warrant specific treatment.

Laboratory Findings

The diagnosis of hemolysis was based on the assessment of several parameters. Unrelated causes of anemia were excluded by other clinical and laboratory investigations.

Low hemoglobin and hematocrit levels may be directly related to intravascular hemolysis and to iron deficiency resulting from the hemosiderinuria complicating this disorder. Urinary hemosiderin is only found when the plasma haptoglobin level is totally depet by the hemolytic process and free hemoglobin is filtered through the glomeruli. The haptoglobin levels have been measured in this series as an index of the degree of hemolysis, and further discussion of their significance will follow.

Other indices of hemolysis include the reticulocyte count as a measure of bone-marrow regeneration and the plasma level of lactic dehydrogenase which is considered the most sensitive index of all and has been shown to have a close correlation with the red cell survival in a similar study. The detection of

Table 1

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/100 ml)</td>
<td>Males 13.5 – 18</td>
</tr>
<tr>
<td></td>
<td>Females 11.5 – 16.5</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>Males 40 – 54</td>
</tr>
<tr>
<td></td>
<td>Females 33 – 47</td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>0.2 – 2</td>
</tr>
<tr>
<td>Serum iron (µg/100 ml)</td>
<td>Males 80 – 175</td>
</tr>
<tr>
<td></td>
<td>Females 60 – 160</td>
</tr>
<tr>
<td>Serum bilirubin (mg/100 ml)</td>
<td>0.2 – 0.9</td>
</tr>
<tr>
<td>Red cell fragmentation (%)</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Plasma lactic dehydrogenase</td>
<td>147 – 305</td>
</tr>
<tr>
<td>(Wroblewski units/ml)</td>
<td></td>
</tr>
<tr>
<td>Plasma haptoglobins (mg/100 ml)</td>
<td>50 – 150</td>
</tr>
</tbody>
</table>
Table 2
Analysis of Hematologic Data in 62 Patients with Aortic Valve Replacement

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Starr-Edwards prostheses (group I)</th>
<th>Fascia lata grafts (group II)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Entire group</td>
<td>Regurgitant</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td>Hemoglobin and hematocrit below normal</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Reticulocyte count above 2%</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Serum iron level below normal</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Hemosiderin present in urine</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Serum bilirubin (mg/100 ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 – 2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Red cell fragmentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 – 2.9%</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>3% and above</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Plasma lactic dehydrogenase (Wroblewski units/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 – 500</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Serum haptoglobins (mg/100 ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent or &lt; 25</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>25 – 50</td>
<td>3</td>
<td>—</td>
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<tr>
<td>&gt; 50</td>
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Table 3
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<table>
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<th>Parameter</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Entire group</td>
<td>Regurgitant</td>
</tr>
<tr>
<td>Hemoglobin (g/100 ml)</td>
<td>14.2 ± 1.7</td>
<td>13.9 ± 1.1</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>41.9 ± 4.7</td>
<td>40.6 ± 2.8</td>
</tr>
<tr>
<td>Reticulocyte count (%)</td>
<td>3.1 ± 2.9</td>
<td>3.1 ± 3.0</td>
</tr>
<tr>
<td>Serum iron (μg/100 ml)</td>
<td>82.6 ± 33.5</td>
<td>79.6 ± 16.2</td>
</tr>
<tr>
<td>Serum bilirubin (mg/100 ml)</td>
<td>0.99 ± 1.75</td>
<td>1.8 ± 3.2</td>
</tr>
<tr>
<td>Red cell fragmentation (%)</td>
<td>0.9 ± 1.8</td>
<td>1.4 ± 1.8</td>
</tr>
<tr>
<td>Plasma lactic dehydrogenase (Wroblewski units/ml)</td>
<td>650 ± 710</td>
<td>804 ± 878</td>
</tr>
</tbody>
</table>

Number of patients                               | 27           | 6           | 21             | 35           | 7           | 28             |

*Statistical significance of the differences between regurgitant and nonregurgitant valves in each group. Values <0.05 are statistically significant.
red cell fragments was the most objective evidence of direct trauma to the red cells.

**Hemoglobin and Hematocrit**

Five patients in each group had hemoglobin and hematocrit levels below normal (table 2). Of these, four in group I and two in group II had nonregurgitant valves. In group I the values were essentially similar in patients with and without regurgitation, while in group II they were significantly lower in patients with regurgitation as compared to those without regurgitation (table 2). The mean values in patients without regurgitation were lower in group I than in group II (table 3).

**Reticulocytes**

Fourteen patients (51.8%) in group I and 10 in group II had reticulocyte counts above 2% (table 2). Five patients in group I and four in group II had counts above 5%. Four of the five in group I and two in group II had nonregurgitant valves. In group I the counts on patients with and without regurgitation were similar, while in group II, patients with nonregurgitant valves had values significantly lower than those with regurgitant valves (table 3 and fig. 2). The mean counts on patients without regurgitation were higher in group I than in group II (table 3).

**Serum Iron**

Ten patients (37%) in group I and six (17.1%) in group II had serum iron levels below normal. Of these, nine in group I and three in group II were nonregurgitant valves (table 2). The values of serum iron in group I were significantly lower than the values in group II (table 3).

**Urinary Hemosiderin**

Hemosiderin was detected in the urine of 10 patients (37%) in group I and in nine (25.7%) in group II. Of these, seven in group I and four in group II had nonregurgitant valves (table 2).

**Serum Bilirubin**

The serum bilirubin level was above 1 mg/100 ml in four patients (14.8%) in group I: of these, one patient had regurgitant and three had nonregurgitant valves. In two patients the values were above 2 mg/100 ml. In group II six patients (17.1%) had values above 1 mg/100 ml. Two of them had regurgitant and four had nonregurgitant valves. Only one patient with a regurgitant valve had a value above 2 mg/100 ml (table 2). The mean values were higher in group I as compared to group II (table 3).

**Red Cell Fragmentation**

Eight patients (33.7%) in group I and six (17%) in group II showed fragmentation of 1% or more of the red cells in thin peripheral blood films (table 2). The mean values were higher in group I as compared with group II (table 3). In group I three patients had regurgitant and five nonregurgitant valves. The highest value was 7.6%. In group II the highest value was 2.5%. Three of the patients in group II had regurgitation, one developed an aortic diastolic murmur subsequently, and the remaining two had associated mitral valve disease.

**Plasma Lactic Dehydrogenase (LDH)**

Plasma LDH levels were high in 22 patients (81.4%) in group I and in 18 patients (51.4%) in group II.

The mean values for LDH were higher in patients with regurgitant compared to those with nonregurgitant valves in both groups (table 3 and fig. 3, top). The LDH values were lowest in the patients with nonregurgitant fascia lata valves. In group I the difference between the regurgitant and nonregurgitant values was not statistically significant while in group II it was statistically significant. The values of LDH in nonregurgitant patients in group I were significantly higher than those in group II (table 3 and fig. 3, top).

**Plasma Haptoglobins**

Plasma haptoglobins were generally low in both groups. In group I they were either absent or below 25 mg/100 ml in 24 patients and between 25 and 50 mg in three
patients; none of them had values above 50 mg. In group II the haptoglobins were absent or below 25 mg/100 ml in 23 patients, between 25 and 50 mg in five, and above 50 mg in seven (table 2).

**Direct Coombs’ Test**

The direct Coombs’ test was negative in all patients, suggesting that there was no immune mechanism involved in the hemolytic process.

**Relation of Hemolysis to Size and Type of Valve Substitute**

To evaluate the probable factors, other than regurgitation, implicated in the production of chronic hemolysis, data on patients without regurgitation in both groups were further analyzed according to the size and type of the valves used (table 4 and fig. 3, bottom). The plasma LDH values were higher in patients with smaller prosthetic valves than in those with the larger ones. However, due to the small number of patients the difference was not statistically significant.

Twenty-one patients in group I had the silastic ball prosthesis while six had the composite seat type of prosthesis. No valid conclusion could be drawn on comparing data from these two groups. A similar analysis in group II did not show any significant difference between the values in patients with small and large grafts or between those with autologous and those with homologous grafts.

Nineteen patients in group II were re-studied 2 to 4 months later. The values obtained on these two investigations were not significantly different.

**Discussion**

Chronic hemolysis is a well-known complication of aortic valve replacement with Starr-Edwards prosthesis.1–8 The occurrence of hemolysis after insertion of homografts9 and heterografts7,10 is reported to be less frequent.
CHRONIC HEMOLYSIS

Figure 2

Reticulocyte counts in patients with regurgitant and nonregurgitant aortic fascia lata grafts. Counts in the regurgitant group are significantly higher. Key to symbols same as in figure 1.

Turbulent flow, obstruction to flow, direct trauma to the red cells, regurgitation through or around the valve, and the presence of foreign material in the bloodstream are some of the important etiologic factors.

A positive direct Coombs' test has been reported on patients after heart valve replacement. Brodeur and associates suggested that this was possibly due to the production of antibodies to the patient's own red cells on the antigenic stimulus of destroyed red cells. In the present study the direct Coombs' test was negative in all cases.

This report indicates that after insertion of frame-mounted fascia lata valve into the aortic position significant intravascular hemolysis occurs only if regurgitation is present. The nonregurgitant fascial grafts are not associated with a significant degree of hemolysis. Similar experience has been reported after the insertion of homografts and heterografts.

In patients with Starr-Edwards prostheses, hemolysis occurs even in the absence of regurgitation as shown in this and other reports. Sometimes the prosthetic valves may have to be removed and replaced because of intractable hemolysis. This happened in two of our patients: at reoperation a perivalvular leak was found in one and in the other the cloth covering the prosthesis had worn off and contained fibrinous deposits. It is possible that a high-velocity jet through a small perivalvular leak is more damaging to red cells than a larger reflux.

It has been suggested that turbulent flow is an important factor causing red cell damage. Our results support this view inasmuch as hemolysis was associated with the small Starr-Edwards valves more often than with the larger ones in the absence of regurgitation.

Since the central flow characteristics of normal aortic valves, aortic homografts, and fascia lata grafts are similar, they behave similarly in respect of hemolysis.

Low serum iron values in patients with Starr-Edwards prostheses probably reflect the depletion of iron due to urinary losses as a result of chronic hemolysis. The serum iron values were significantly lower in patients with Starr-Edwards prostheses than in patients with fascia lata valves.

The most direct evidence of injury to the red cells apparently is the finding of fragmented red cells in blood smears. The presence of one or more fragmented red cell per 100 normal cells seems to be significant evidence of intravascular red cell destruction. In the fascia lata group only six patients showed 1% or more red cell fragmentation. Three of them had regurgitant valves, and one developed an aortic diastolic murmur subsequently. It is possible that this patient had clinically undetectable regurgitation, at the time of the investigation. The other two patients had
Values for plasma lactic dehydrogenase (L.D.H.) (Top) In all 62 patients with aortic valve replacement. Values for patients with regurgitant valves are higher than those for patients with nonregurgitant valves in both groups, and in patients with fascia lata grafts this difference is statistically significant. Patients with nonregurgitant Starr-Edwards prostheses have values sig-
Table 4

Comparison of Hematological Data in Patients with Nonregurgitant Valves according to Size

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Starr-Edwards prostheses (group I)</th>
<th>Fascia lata grafts (group II)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small Mean ± sd</td>
<td>Large Mean ± sd</td>
</tr>
<tr>
<td>Hemoglobin (g/100 ml)</td>
<td>13.7 ± 2</td>
<td>14.8 ± 1.5</td>
</tr>
<tr>
<td>Hmatocrit (v/v)</td>
<td>40.6 ± 5.6</td>
<td>43.1 ± 3.9</td>
</tr>
<tr>
<td>Reticulocyte count (v/v)</td>
<td>3.19 ± 3.95</td>
<td>3.0 ± 1.8</td>
</tr>
<tr>
<td>Serum iron (µg/100 ml)</td>
<td>86.4 ± 47.5</td>
<td>80.2 ± 23.9</td>
</tr>
<tr>
<td>Serum bilirubin (mg/100 ml)</td>
<td>1.0 ± 1.3</td>
<td>0.4 ± 0.3</td>
</tr>
<tr>
<td>Red cell fragmentation (v/v)</td>
<td>1.26 ± 2.4</td>
<td>0.11 ± 0.33</td>
</tr>
<tr>
<td>Plasma lactic dehydrogenase (Wroblewski units/ml)</td>
<td>812 ± 889</td>
<td>387 ± 94</td>
</tr>
</tbody>
</table>

Number of patients

<table>
<thead>
<tr>
<th>Small</th>
<th>Large</th>
<th>Small</th>
<th>Large</th>
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<tbody>
<tr>
<td>11</td>
<td>9</td>
<td>12</td>
<td>16</td>
</tr>
</tbody>
</table>

associated mitral valve disease. In one of them
the mitral valve was repaired, and the red cell
damage was probably due to residual mitral
incompetence.

Myhre and associates6,21 reported a close
correlation between the lactic dehydrogenase
activity and the half-life of 51Cr-labeled red
cells in similar studies for hemolysis. In our
patients the mean values of LDH were higher in
regurgitant valves in both groups. Patients
with nonregurgitant Starr-Edwards prostheses
had significantly higher values compared to
those with nonregurgitant fascial grafts. The
mean values were higher in patients with
small Starr-Edwards valves as compared to
those with the larger valves in the absence of
regurgitation. Myhre and associates6 also
found raised LDH values in patients with
smaller valves.

Low values for haptoglobins have been
reported to be a sensitive index of hemolysis.28,24
In our series the haptoglobins were
found to be low in those patients who had no
other evidence of hemolysis. It is possible that
these patients had an insignificant degree of
hemolysis not detectable by the other methods
used. Yacoub and associates9 have reported
similar low values of haptoglobins in patients
with homograft aortic valves who had no
hemolysis detectable by other criteria including
red cell survival studies. They indicated
that in their patients the hepatic synthesis of
haptoglobins was probably impaired.

The degree of hemolysis may tend to
remain stationary, but in some patients it may
lessen. One of our patients with Starr-
Edwards prosthesis and a perivalvular leak
had a severe degree of hemolysis which has
regressed dramatically. The mechanism of this
improvement is not clear. It seems possible
that with the passage of time endothelializa-
tion of the cloth covering of the valve seat was
associated with reduction in hemolysis. In
most of the patients hemolysis does not seem
to increase and they appear to respond to iron
therapy. In a few cases, however, there is
progressive hemolysis which may require
replacement of the valve.8,5 Two of our
patients in this series had Starr-Edwards
valves replaced for this reason.

**CHRONIC HEMOLYSIS**

_**Table 4**_

**Comparison of Hematological Data in Patients with Nonregurgitant Valves according to Size**

<table>
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<tr>
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<th>Starr-Edwards prostheses (group I)</th>
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</tr>
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<td>Small Mean ± sd</td>
<td>Large Mean ± sd</td>
</tr>
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<tbody>
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<td>16</td>
</tr>
</tbody>
</table>

significantly higher than those with nonregurgitant fascia lata grafts (P < 0.05). (Bottom) In
patients with nonregurgitant valves according to valve size. Patients with smaller valves have
higher values for L.D.H. than those with larger valves in group I (Starr-Edwards prostheses).
However, the difference is not statistically significant. The mean value is highest in patients
with small Starr-Edwards prostheses. The values in group II (fascia lata grafts) are essentially
similar for patients with small and large grafts. Key to symbols same as in figure 1.

_Circulation, Volume XLVI, August 1972_
From the results obtained in this series, it is concluded that after aortic fascia lata valve replacement significant hemolysis only occurs if the patient develops regurgitation. In contrast, in patients with Starr-Edwards prostheses hemolysis occurs even without regurgitation. The flow characteristics of biologic tissue valve grafts are similar to normal aortic valves and they appear to have few hemolytic complications in the absence of regurgitation. On the other hand, hemolysis following the insertion of aortic Starr-Edwards prostheses may sometimes be so severe as to necessitate removal of the valve even when there is no regurgitation.

Acknowledgment

The authors are grateful to the staff of the Departments of Biochemistry and Haematology for their help with this investigation, to Miss Beryl Walsh for photographic work, and to Mrs. Judith Ladley for secretarial help.

References


Chronic Hemolysis following Fascia Lata and Starr-Edwards Aortic Valve Replacement
KAMAL S. DAVE, CHAND K. MADAN, BROJESH C. PAKRASHI, BRYON E. ROBERTS and MARIAN I. IONESCU

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