Hemolytic Syndrome Following the Insertion of a Lucite Ball Valve Prosthesis into the Cardiovascular System

By Frederick Stohlman, Jr., M.D., Stanley J. Sarnoff, M.D., Robert B. Case, M.D. and Arthur T. Ness, Ph.D.

Permanent bypass of the aortic valve was accomplished in the dog by placing a lucite conduit containing a Hufnagel valve between the left ventricular apex and thoracic aorta. Red cell destruction was produced by the valve in this position and was accompanied by hemoglobinemia, hemoglobinuria, anemia, reticulocytosis and renal hemosiderosis. Red cell survival, as determined with Cr,

was markedly shortened.

The development of a lucite ball valve prosthesis by Hufnagel1 has made possible significant advances in the field of cardiac surgery. This prosthesis originally was inserted in the thoracic aorta distal to the left subclavian artery in an effort partially to correct the regurgitation of aortic insufficiency. More recently an operation for the correction of an artificially induced aortic stenosis in the dog with a prosthesis containing such a lucite ball valve* has been described by Sarnoff, Donovan, and Case.2 The prosthesis was inserted between the apex of the left ventricle and the thoracic aorta. Following this procedure the cardiac output (minus coronary flow) enters the aorta via the apical-aortic anastomosis. During the course of postoperative studies it was noted that these dogs developed hemoglobinemia, hemoglobinuria, and anemia. Preliminary observations have been reported elsewhere.3 In this paper observations on the red blood cell destruction occurring after insertion of the lucite ball valve prosthesis are reported.

Methods and Materials

Studies have been carried out on a total of 15 dogs; in 8 dogs throughout their postoperative course and in 12 dogs at periods from one to 10 months postoperatively. The dogs weighed from 16 to 25 Kg. The description of the prosthesis and technique of insertion has been published previously.4 Hemtocrits were determined by the method of Strumia4 and reticulocytes were stained with new methylene blue,5 and enumerated as described by Brecher and Schneiderman.6 Plasma hemoglobin was determined by the method of Bing and Baker.7 Normal values in this laboratory are 40 to 55 per cent for the hematocrit and 0.1 to 0.7 per cent for the reticulocyte count. Plasma hemoglobin, collected in the manner used in this study, was found to be up to 20 mg. per 100 cc. in control dogs. Significance was not attributed to plasma hemoglobin levels of less than 30 mg. per 100 cc. Urine was tested for hemosiderin with the Prussian-blue reaction. The methods employed in the estimation of red cell survival with Cr8 following auto- and homo-transfusion and the data on which normal values in the dog are based are given elsewhere.9 Donors and recipients were compatible for the known canine agglutinogens.9

Results

All 15 dogs studied showed evidence of increased red cell destruction following the introduction of the lucite ball valve prosthesis in the apical-aortic position.

1) Changes in Hematocrit, Reticulocyte Count, and Plasma Hemoglobin During the Postoperative Period. Eight dogs have been followed for 5 to 84 days after operation. The changes shown in figure 1 are representative of the ranges encountered in this group. In the first 6 to 10 days, a sharp decline in hematocrit occurred in all dogs except dog 15 (fig. 1). Thereafter the course varied. In two dogs, the hematocrit rose briefly and then declined to

586 Circulation, Volume XIII, April, 1956
levels of 20 to 25. These dogs subsequently required transfusion for survival (dogs 10 and 17, fig. 2). In two other dogs the hematocrit stabilized between 30 and 35. One dog showed a return to normal values (dog 13, fig. 2). Two dogs died after operation, one on the fifth day and the other on the twelfth, with hematocrits of 33 and 17, respectively, (dog 16, fig. 1).

Reticulocytosis became apparent on the third to the fifth day in all eight dogs studied. There was a close correlation between the severity of anemia and the degree of reticulocytosis (figs. 1, 2 and 3).

Striking hemoglobinemia and hemoglobinuria, indicating intravascular hemolysis, were observed in all dogs. Maximum plasma hemoglobin levels varying from 180 to 800 mg. per 100 cc. were observed on the first or second postoperative day in the six dogs in which it was determined.

In addition to the studies mentioned above, a simple 2-inch lucite tube was substituted for a segment of thoracic aorta in four dogs. A slight and transient reticulocytosis and fall in hematocrit, compatible with blood loss incident to operation, were observed following this procedure. Plasma hemoglobin levels remained below 10 mg. per 100 cc.

(2) Long Term Observations on the Course of Anemia. The course of the anemia in seven dogs for periods up to 10 months are shown in figures 2 and 3. These are representative of the 12 dogs so studied. It is evident that red cell destruction by the valve continued over the period of observation and that there was a considerable variability in this phenomenon. Reticulocyte values remained elevated above the normal of 0.1 to 0.7 per cent even in those dogs in which the hematocrit had returned to normal. Transfusion has been required (figs. 2 and 3) at frequent intervals to maintain three of the dogs studied.

In those dogs with more severe hemolytic states, plasma hemoglobin values ranging from 75 to 280 mg. per 100 cc. were observed throughout the period of study. In those dogs whose hematocrits were above 35, intermittent hemoglobinemia has been observed with values ranging up to 75 mg. per 100 cc. Gross hemosiderinuria has been observed in all dogs.
Three dogs died nonrenal deaths during the period of study and a fourth died of unknown causes. In these four dogs, whose hematocrits were 20, 22, 37 and 45, heavy deposits of hemosiderin were found in the kidney, primarily in the proximal convoluted tubule (fig. 4).

(3) Red Cell Survival. Shortened red cell survival furnished further evidence of hemolysis. Survival of normal red cells from a single compatible donor was studied in six dogs at periods of three weeks to seven months following insertion of the prosthesis. Hematocrit values in these animals ranged from 20 to 47. In figure 5, the survival of normal donor cells in four of these animals is shown. The survival of red cells in the two other dogs was almost superimposable on the curves of dogs 1 and 3. It is evident that there is marked shortening of survival, the apparent half time varying from 3 to 10 days as compared with the normal value of 21 to 30 days (8). Estimates of the rate of random loss of Cr\textsuperscript{51} per day from hemolysis and elution ranged from 7 to 25 per cent. Normally there is an elution of 1 to 2 per cent of the remaining Cr\textsuperscript{51} from the surviving cells.\textsuperscript{8} Red cell survival following autotransfusion was also shortened in the three dogs so studied. From these data it is clear that, on the average, the rate of red cell destruction was increased several fold.

### Table 1—Correlation of Red Cell Survival, Hematocrit and Reticulocyte Count in Six Dogs with a Lucite Apical-Aortic Anastomosis

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Apparent Cr\textsuperscript{51} Half-time Days</th>
<th>Hematocrit %</th>
<th>Reticulocyte Count %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.0</td>
<td>21.0</td>
<td>15.0</td>
</tr>
<tr>
<td>7</td>
<td>3.0</td>
<td>25.0</td>
<td>9.6</td>
</tr>
<tr>
<td>3</td>
<td>4.5</td>
<td>34.5</td>
<td>3.5</td>
</tr>
<tr>
<td>6</td>
<td>5.0</td>
<td>30.8</td>
<td>8.2</td>
</tr>
<tr>
<td>5</td>
<td>7.0</td>
<td>39.8</td>
<td>4.1</td>
</tr>
<tr>
<td>4</td>
<td>10.0</td>
<td>45.5</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Hematocrit and reticulocyte count are expressed as mean values during the period of study of red cell survival.
As might be expected there was a correlation between the severity of the anemia and the shortening of apparent red cell half time (table 1). This relationship is consonant with the evidence presented in the foregoing sections, namely that the anemia is a consequence of shortened red cell survival.

**Discussion**

An increased rate of red cell destruction has been found in all dogs following the insertion of a lucite apical-aortic anastomosis containing a Hufnagel ball valve. The evidence for hemolysis has consisted of a postoperative fall in hematocrit, reticulocytosis, and a shortened red cell life span, accompanied by hemoglobinemia, hemoglobinuria, and hemosiderinuria. There were also heavy tubular deposits of hemosiderin in the kidneys. The degree of hemolysis has varied in severity. Where the hemolytic process was relatively mild, the increased rate of production of red cells was sufficient to compensate for the hemolysis and the hematocrit returned to normal following the initial decline. In the others anemia has persisted accompanied by marked reticulocytosis, hemoglobinemia, and in some instances, hemoglobinuria.

There is little doubt that hemolysis in these animals is related to the prosthesis. It appears likely that red cells traumatized by contact between the rigid ball and rigid valve housing are damaged or destroyed. Since hemoglobinemia is present, it is evident that many of these are destroyed intravascularly; perhaps others suffering less damage at the time of impact may be removed extravascularly. The possibility was considered that chemical injury to the red cell resulting from contact with some constituent of the plastic accounts for the hemolysis. However, the results of studies on dogs following the insertion of a simple lucite tube in the aorta are inconsistent with the latter explanation.

Many factors undoubtedly play a role in establishing the rate of hemolysis in an individual dog. Older cells which are mechanically more fragile, are undoubtedly destroyed more rapidly and this at least in part may account for the peak hemoglobinemia occurring in the immediate postoperative period. Subsequently there are few cells greater than 50 days old and difference in fragility, due to age of cells, is probably of less importance. The difference in survival of blood from a single donor in six recipients with valves would seem to exclude the inherent fragility of the red cell as a significant factor.

Other factors, such as the magnitude and the rate of change of the pressure gradient across the valve, which determine the impact force of the ball, are of greater significance. When the conventional Hufnagel valve is placed in the descending aorta for the treatment of aortic insufficiency, it may be expected that the impact force of the ball will be less, and thereby the extent of hemolysis correspondingly diminished. Nevertheless a fall in hematocrit was noted by Rose and coworkers in nine patients in whom the conventional Hufnagel valve had been inserted for aortic regurgitation. The hematocrit on an average fell to 34.8 from a preoperative level of 41.5. It is likely that these were not the lowest hematocrits exhibited by these patients since these values were determined between the fourteenth and thirty-sixth postoperative day (average 24.2). It is a safe assumption that by the fourteenth day increased red cell production had already begun to compensate for the induced anemia (fig. 2). Alterations in plasma volume were not responsible for the lowered hematocrits since in those patients there was no significant change of plasma volume. It seems reasonable to suggest on the basis of the present report that an increased rate of red cell destruction may be responsible for at least part of the postoperative decline in hematocrit.

It has recently been made clear that one of the important compensatory responses to anemia is coronary vasodilation and a consequent increase in coronary flow to provide the oxygen required by the myocardium. It was also demonstrated that, in the presence of coronary insufficiency, degrees of anemia which are ordinarily well tolerated by the myocardium depress myocardial function. The frequency with which angina pectoris presents itself as a prominent part of the symptom complex in aortic regurgitation together with the known
low aortic diastolic (coronary perfusion) pressures make it very likely that coronary insufficiency is an important component in this disease. It is suggested, therefore, that in these patients even slight degrees of anemia be carefully avoided. This should be particularly watched for in the immediate postoperative period after the placement of the Hufnagel valve, especially since coronary perfusion pressure is substantially decreased following this procedure. Put in other terms, the coronary vessels should not be required to dilate in response to anemia, whatever the cause may be, when in all likelihood, they are already maximally dilated because of the low coronary perfusion pressure.

Data collected subsequent to the investigations cited above appear to clarify certain aspects of the overall problem. Some of the apical-aortic prostheses which had been used in the above experiments were segmented so as to obtain conventional Hufnagel valves. These were then placed in the thoracic aorta below the left subclavian artery in dogs in which moderate aortic insufficiency had been produced.* In 3 of the 5 dogs studied there was a mild increase in the rate of red cell destruction. In these dogs the insufficiency proximal to the valve was moderate whereas in those with the apical-aortic by-pass there was virtually complete insufficiency proximal to the valve. Thus, the position of the ball-valve in large measure determines its effect on the survival of red cells. Presumably, the degree of insufficiency which determines the rate of change of the pressure gradient across the valve and, therefore, its velocity and impact force upon seating, is the determining factor. The rate of change of the pressure gradient across the valve and the consequent impact force of the ball would be even greater in the atrioventricular position.

The above data do not in any way constitute a contraindication to the use of the lucite ball-valve prosthesis in the conventional Hufnagel position provided that the immediate postoperative decline in hematocrit be avoided. They do, however, strongly suggest that the lucite ball-valve is unsuitable for use in direct continuity with cardiac chambers.

More recent efforts have been devoted to the development of an elastic silicone valve in the hope that the more resilient housing would absorb some of the impact force of the ball. The data thus far are encouraging and indicate a substantial decrease in red cell destruction to a level which may be satisfactory for clinical use in the apical-aortic position.

**Summary**

The insertion of a lucite prosthesis containing a Hufnagel ball valve between the apex of the left ventricle and the thoracic aorta has led to the development of an anemia, accompanied by hemoglobinemia, hemoglobinuria, hemosiderinuria and a markedly shortened red cell life span. The hemolytic process apparently results from mechanical trauma to the red cells by the impact of the rigid ball against the rigid valve housing. Such a valve is not suitable for use in direct continuity with the cardiac chambers.

**Summario in Interlingua**

Le placiamento del valvula aortic in derivatio permanente eseva effectuate in canes per le installation de un conducto de Lucite, contiente un valvula de Hufnagel, inter le apice sinistro-ventricular e le aorta thoracice. Le valvula causava destruction de erythrocytos. Isto eseva accompaniate de hemoglobinemia, hemoglobinuria, anemia, reticuloeytosis, e hemosiderosis renal. Le superviventia del erythrocytos, determinate per medio de Cr, eseva marcatamente reduce. Un tal valvula non es usabile in continuatate directe con le cameras cardiac.

**REFERENCES**

3. **Stohlman, F., Jr., Sarnoff, S. J. and Case, R. B.:** Hemolytic syndrome following insertion of


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