Red Blood Cell Survival in Patients with Aortic Valvular Disease and Ball-Valve Prostheses

By Michael T. H. Brodeur, M.D., C.M., Donald W. Sutherland, M.D., Robert D. Koler, M.D., Albert Starr, M.D., Jean A. Kimsey, B.S., and Herbert E. Griswold, M.D.

We have observed three patients who had developed severe hemolytic anemia following aortic valve replacement with a Starr-Edwards ball valve. The anemia has persisted from 3 to 6 months following operation.

Hemolytic anemia following repair of os- tum primum defect with a Teflon patch with a regurgitant jet through the mitral cleft has been described. Hemolytic anemia following insertion of a Lucite ball-valve into the aorta has been described in dogs. Scattered reports are now beginning to appear describing hemolytic anemia following aortic valve replacement. Intracardiac and valvular turbulence with mechanical damage to the red blood cells was suggested as a possible mechanism for the anemia in these cases.

This paper reports studies of the red blood cell survival in a number of patients with aortic valvular disease, with aortic valve replacement, and with multiple valve replacement to determine if the ball-valve prosthesis has hemolytic properties that predispose to the development of hemolytic anemia.

Methods and Investigations

Red blood cell survival was measured in 20 normal subjects, in 21 patients with aortic valve disease, in 12 patients following aortic valve replacement, four of whom were studied preoperatively, and in seven patients following multiple valve replacement, two of whom were studied preoperatively. Cardiac catheterization was done the same day that survival studies were started in all cases except five. These five studies were all done postoperatively and, as was true for all postoperative survival studies, were begun 3 to 12 months after surgery.

Red blood cell survival was determined with radioactive sodium chromate essentially by the method of Gray and Sterling. The patient's heparinized red cells were labeled in vitro with 100 microcuries of sodium chromate. After incubation for a period of 30 minutes at 37°C, the sodium chromate was reduced to chromic chloride by the addition of 50 mg. of ascorbic acid. The blood was then spun down at 1,000 revolutions per minute for 10 minutes and the plasma was removed. The red cells were washed twice and reconstituted to their original volume with sterile saline. Twenty milliliters were then reinjected intravenously. The first sample was obtained 15 minutes after injection of the labeled cells. Subsequent samples were obtained at least three times a week for 2 weeks and then once a week for 3 weeks. The radioactivity of these samples was compared with the radioactivity of the 15-minute sample. The conventional half-survival time of labeled cells is that time when the ratio of observed activity to initial activity reaches 50 per cent.

In most patients there was an initial rapid loss of some of the labeled cells followed by a slower loss of labeled cells from the circulation. The double exponential curve which resulted when the activity of the labeled cells was plotted on semilogarithmic paper has been described mathematically by Rigas. We have analyzed our results by his equation (fig. 1).

\[
\frac{A_t}{A_0} = \left(1 - \frac{t}{L}\right) \left[ C_1 e^{-\lambda t} + (1 - C_1) e^{-\mu t}\right]
\]

where:

- \(A_t\) = radioactivity of the sample at time \(t\).
- \(A_0\) = radioactivity of the 15-minute sample.
- \(L\) = mean red cell lifespan (taken as 120 days).
- \(C_1\) = initial fraction of the labeled cells removed.
- \(\lambda\) and \(\mu\) are the rate constants.

From the divisions of cardiology and experimental medicine of the department of medicine, and the division of cardiopulmonary surgery, department of surgery, university of Oregon medical school, Portland, Oregon.

Supported by a program project grant of the U. S. Public Health Service (HE 06336-03) and by AEC contract AT (45-1)-581.
RED BLOOD CELL SURVIVAL

Figure 1

Computer analysis of red blood cell survival. $A_t =$ radioactivity of sample at time $t$. Expressed as counts per minute per 2 ml. whole blood. $A_o =$ radioactivity of 15-minute sample. Expressed as counts per minute per 2 ml. whole blood. $C_i =$ proportion of initial rapidly destroyed red cells compared to total red cell population. $r_1 =$ exponential which describes rate of random loss of chromium label due to elution and/or random destruction of the initial red cell population. $r_2 =$ exponential which describes rate of random loss of label due to elution and/or random destruction of the principal red cell population. $T/2 =$ red cell half-life, i.e., time required for $A_t/A_o$ to reach 0.5 in the semilogarithmic scale.

$C_i =$ the proportion of the initial rapidly destroyed red cells compared to the total red cell population. Also referred to as a subpopulation of rapid randomly destroyed cells.

$r_1 =$ rate of random loss of label due to elution or random destruction of the initial red cell population.

$r_2 =$ rate of random loss of label due to elution or random destruction of the remaining red cells.

The values for $A_t$ and $A_o$ expressed as counts per minute per 2 ml. of whole blood were determined by a scintillation detector with a 2-inch sodium iodide crystal. The values for the constants $C_i$, $r_1$, and $r_2$ were obtained from a Scientific Data Systems 920 computer. The red cell survival at any day can be calculated by the values found for these constants. The observed red blood cell activity ($A_t/A_o$) at time $t$ plotted as the ordinate on semilogarithmic paper against time in days on the abscissa corresponded well with the values obtained from the equation. The parameters $C_i$, $r_1$, and $r_2$ from this equation were more meaningful than the estimate of $T/2$, particularly when there was a rapid initial loss of radioactivity and the resulting curve was nonlinear. Because of short periods of observation and technical sources of variation, estimates of the mean lifespan ($L$) were variable and the theoretical value of 120 days was used to fit all estimates of $C_i$, $r_1$, and $r_2$. Physiologic sources of variation were minimized by starting the studies when the patients were not in congestive failure. Blood volumes were determined as part of the initial Cr51 labeling procedure by comparing the radioactivity of the 15-minute sample with a 1:250 dilution of an aliquot of the labeled cells.15 Serial venous hematocrit levels were measured in cases 42 to 49, 66, and 67 and showed no significant variation during the course of the survival studies.16

Cardiac catheterization was performed with transseptal puncture in all patients except those
having more than one prosthesis. In these patients the left ventricle was entered by direct percutaneous puncture. None of the patients studied had any hemorrhagic complications from the procedure. Other studies included complete blood count, reticulocyte count, osmotic and mechanical fragility, and estimates of red blood cell sequestration in liver and spleen. The antiglobulin (Coombs) procedures were done by the standard tube method. Antiglobulin sera was produced in this laboratory by immunizing rabbits with a human serum protein fraction containing 80 per cent gamma globulin, 15 per cent beta globulin, and 5 per cent alpha globulin. The antisera obtained were absorbed and diluted in the usual fashion to produce a standard Coombs reagent. Direct antiglobulin tests were carried out with undiluted 1:4, 1:16, and 1:64 dilutions of this standard reagent in order to avoid a prozone phenomenon.

Results

In none of the patients studied was there evidence of abnormal mechanical or osmotic fragility of the red cells, nor abnormal red blood cell sequestration in the spleen or liver. The total blood volume was within the normal range in all patients when the studies were started.

Normal Subjects

Red cell survivals were performed in 20 normal subjects (table 1). The mean T/2 cell survival was 27 days, with a range from 24 to 32 days. No one exhibited a second population of more rapidly destroyed red cells (C1 and r1). The values for C1 and r1 were zero in each person. The mean rate of destruction (r2) of the normal red cells was 1.75 per cent of the cell population per day. The 95-per cent range was 1.25 to 2.25 per cent.

Aortic Valve Disease

We were surprised to find that the majority of preoperative patients with aortic valvular disease, although not anemic, had shortened red cell survivals (table 2). Eighteen of the 21 patients had a T/2 of 24 days or less. The mean T/2 was 20 days, with a range of 14 to 26 days (figs. 2 and 3). Values for C1, r1, and r2 were obtained in all patients (table 2). Seventeen patients had evidence for a second population (C1) of more rapidly destroyed red cells. The mean value for the rate of destruction of the remaining population of red cells, r2, was 2.18 per cent per day. Nine patients exhibited rates of destruction (r2) greater than 2.25 per cent per day, that is, greater than two standard deviations from the mean normal rate of destruction.

Five patients failed to show a second population (C1) of rapidly destroyed red blood cells. Four of these had normal red cell survivals. The fifth patient (case 18) had a shortened T/2 of 17 days due to accelerated rate of destruction (r2) of her single population of red cells of 3.63 per cent destroyed each day.

There was no correlation demonstrated between the red blood cell survival and the severity of the valvular disease as determined by the magnitude of the transvalvular aortic systolic pressure gradient, the calculated valve area, the cardiac output, the stroke volume, or the presence or absence

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*± 2 standard deviations.

N, number of cases; T/2, half-life of tagged red cells (days); C1, rapidly destroyed cells expressed as a proportion of total red cell population; r1, rate of destruction of C1 (proportion per day); r2, rate of destruction of principal cell population (proportion per day).
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<th>C1</th>
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T/2, half-life of tagged red cells (days); C1, rapidly destroyed cells expressed as a proportion of total red cell population; r1, rate of destruction of C1 (proportion per day); r2, rate of destruction of principal cell population (proportion per day); CI, cardiac index (L./M. 2 × min); D, dye; F, Fick; LV, left ventricle; BA, brachial artery; AI, aortic insufficiency; AS, aortic stenosis; MI, mitral insufficiency; MS, mitral stenosis; TI, tricuspid insufficiency; TS, tricuspid stenosis; PDA, patent ductus arteriosus.
of valvular calcification. Red cell survivals were found to be shortened in patients with aortic stenosis and in patients with aortic insufficiency.

**Aortic Valve Replacement**

The red blood cell survival was determined in 12 patients after aortic valve replacement (table 3). Values for T/2 ranged from 9 to 26 days (figs. 2 and 3). All of these patients had values determined for C₁, r₁, and r₂ (table 3). Ten patients had a second
population (C₁) of more rapidly destroyed red cells. Four of these had values for T/2 greater than 23 days. The other two patients had shortened red cell survivals with evidence that their single population of cells was being destroyed more rapidly than normal (r₂).

There were three patients with a prosthetic valve who were anemic. Case 2 had a hematocrit level of 35 per cent with a reticulocytosis and a T/2 of 16 days. Clinically he had mild aortic regurgitation. Case 24 was complicated by long-standing iron-deficiency anemia. Her low hematocrit value was due to accelerated red blood cell destruction and iron deficiency. There was no evidence of prosthetic valve malfunction. Patient 38 had a severe hemolytic anemia with a hematocrit level of 29 per cent and a T/2 of 9 days. Computer analysis of his erythrocyte survival data showed that 11 per cent of the red cells (C₁) were being destroyed at 26 per cent (r₁) per day and the remainder of the red blood cell population had a slightly accelerated rate of destruction (r₂) of 1.97 per cent per day. He was found to have moderate aortic regurgitation around his prosthetic valve with a grade-III immediate diastolic murmur along the left sternal border but no peripheral signs of aortic insufficiency.

Multiple Valve Replacement

There were seven patients in this group (table 4). Six patients had aortic and mitral valve prostheses; one had aortic, mitral, and tricuspid valve prostheses. The range for T/2 was 16 to 25 days (figs. 2 and 3). Five were found to have a second population (C₁) of more rapidly destroyed red cells.

Three patients (7, 43, and 51) were found to have leaks around prostheses. Patient 7, the only one with triple valve replacement, was anemic, had a transiently positive Coombs test, and will be described in more detail later. Patient 43 had a hematocrit value of 33, a reticulocytosis and a T/2 of 18 days. Cardiac catheterization was compatible with regurgitation around the mitral prosthesis. Patient 51 had regurgitation around the aortic prosthesis and a T/2 of 16 days.

Comparative Study in the Same Patients before and after Operation

Five patients were studied preoperatively; and then restudied after insertion of valve prostheses. In four the aortic valve was replaced; in the fifth both the aortic and mitral valves were replaced. In all of the single valve replacements T/2 was increased after surgery despite minimal aortic insufficiency in case 46. Case 51, with mitral and aortic prostheses, had regurgitation around the aortic prosthesis. In contrast to the other patients in this group the postoperative value for T/2 was shorter than preoperatively (table 5). The decreased T/2 was explained by a postoperative increase in C₁ (population of more rapidly destroyed cells). The other four patients had similar values for C₁ in the two periods (fig. 4).

Cross Circulation Study

Normal cells from a compatible donor injected into a patient with an aortic valve replacement (case 10) were found to have a T/2 of 20 days. The T/2 of the patient’s cells in his own circulation was 18 days. His labeled cells injected into a normal recipient had a T/2 of 20 days (table 6). In each case there was a subpopulation of more rapidly destroyed cells (C₁).

Coombs Test

The Coombs direct antiglobulin test was positive in three patients. Case 36, with aorto valvular disease, had a positive Coombs test with a T/2 of 25 days and was not anemic. He did not have a second population (C₁) but did have a slightly accelerated rate of destruction (r₂) of the single population of cells. Case 7 developed a transiently positive Coombs test after triple valve replacement. His hematocrit level was 29 per cent with a T/2 of 16 days in the postoperative period. The anemia remitted spontaneously by the time of reoperation to correct regurgitation around the tricuspid and mitral prosthetic valves. At the time of this operation the patient’s Coombs test was negative. The T/2 was redetermined 4 months after this operation and was found to be 20 days. The hema-
### Table 4

**Red Cell Survival Studies in Patients with Multiple Valvular Prostheses**

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<th>r2</th>
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Comparison of Red Cell Survivals before and after Operation in the Same Patients

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<td>(6) Preop*</td>
<td>51 F</td>
<td>38</td>
<td>0.9</td>
<td>24</td>
<td>.0294</td>
<td>1.7650</td>
<td>.0202</td>
<td>11</td>
<td>AS, AI</td>
<td>Normal prosthesis</td>
</tr>
<tr>
<td>(15) Preop</td>
<td>53 F</td>
<td>39</td>
<td>0.8</td>
<td>20</td>
<td>.2115</td>
<td>1.073</td>
<td>.0141</td>
<td>4</td>
<td>AS, AI</td>
<td>Normal prosthesis</td>
</tr>
<tr>
<td>(12) Preop</td>
<td>49 M</td>
<td>44</td>
<td>1.7</td>
<td>24</td>
<td>.1266</td>
<td>.1685</td>
<td>.0125</td>
<td>3</td>
<td>AS, AI</td>
<td>Normal prosthesis</td>
</tr>
<tr>
<td>(11) Preop</td>
<td>38 F</td>
<td>36</td>
<td>2.1</td>
<td>25</td>
<td>.0622</td>
<td>1.2453</td>
<td>.0238</td>
<td>8</td>
<td>AS, AI</td>
<td>Probable mild AI</td>
</tr>
<tr>
<td>51†</td>
<td>36 M</td>
<td>37</td>
<td>1.5</td>
<td>19</td>
<td>.0903</td>
<td>.4552</td>
<td>.0242</td>
<td>4</td>
<td>AI, MS, MI</td>
<td>Leaky aortic prosthesis</td>
</tr>
</tbody>
</table>

T/2, half-life of tagged red cells (days); C₁, rapidly destroyed cells expressed as a proportion of total red cell population; r₁, rate of destruction of C₁ (proportion per day); r₂, rate of destruction of principal cell population (proportion per day); AS, aortic stenosis; AI, aortic insufficiency; MS, mitral stenosis; MI, mitral insufficiency.

*Figures in parentheses are preoperative case numbers.
†Double valve replacement.

Discussion

Stohlman and associates described a hemolytic syndrome in dogs after the insertion of a disk containing quartz beads. This conclusion was probably not the cause of the hemolysis, since it is further supported by Fleisch, who produced hemolysis with a rotating cylinder in a blood sample.

They suggested that hemolysis was probably produced directly by currents and turbulence in the blood as a result of the rotating cylinder. This conclusion was probably not the cause of the hemolysis, since it is further supported by Fleisch, who produced hemolysis with a rotating cylinder in a blood sample.

Preoperative Postoperative

Comparison of red cell half-life before and after operation

Patient 49 had a positive Coombs test after aortic and mitral valve replacement. T/2 was determined to be 22 days after operation and was negative.

T/2 at days

Coombs positive

Coombs negative
Cases of hemolytic anemia following incomplete repair of ostium primum defects have been described by several authors. These patients had the common finding of a residual cleft in the mitral valve, which allowed a jet of blood to regurgitate against the interatrial septum during systole. The hemolytic anemia was corrected in one case by covering the Teflon patch of the repaired atrial septal defect with endocardium. It was corrected in the other case by repair of the mitral regurgitation.

We found that the majority of patients with aortic valvular disease had a slightly shortened red blood cell survival. Most of these patients exhibited red blood cell population with two rates of destruction as indicated by the reported values for \( C_1, r_1 \) and \( r_2 \). Thus it appears that most patients with aortic valvular disease display a second subpopulation of more rapidly destroyed (\( C_1, r_1 \)) red cells. Although none of the patients with aortic valve disease was anemic, one patient had findings compatible with a compensated hemolytic anemia. Thus it is conceivable that patients with aortic valvular heart disease could become anemic on the basis of traumatic hemolysis of red cells. Since most of the random destruction of the initial subpopulation of cells (\( C_1 \)) appeared to occur in the first few days and much of it in the first 24 hours, it might be argued that this phenomenon was an artifact due to the labeling, washing, or injection of the cells. If this were so it would be expected to occur in the normal control group. No values were found for \( C_1 \) and \( r_1 \) in computer analysis of the 20 normal subjects, and their red cell survival was described adequately by a single exponential

\[
\frac{A_0}{A_t} = 1 - \frac{t}{T_2} e^{-rt/2}, \quad 14, 23, 24
\]

Mollison and other investigators, who have performed Cr 51 tagging of cells in ACD solution or heparinized blood of normal individuals, found that there is a rapid initial loss of chromium in the first 24 hours equivalent to the destruction of an average of 6 per cent of the injected cells. This initial loss of chromium was not found in any of our normal controls and is not explained by any difference in technic of preparing or handling the cells.

When patients who had prosthetic replacement of the aortic valve were studied, the red blood cell survival was shortened by an amount similar to those cases with aortic valvular disease. The values for \( T/2, C_1 \), and \( r_1 \) were very similar in those cases of aortic valve replacement not complicated by regurgitation. It is as if one turbulence or current-producing situation had been replaced by another in the postoperative period, so that the same destructive forces were being applied to the red blood cell membrane to cause increased red cell destruction.

Under these conditions of a pre-existing shortened red blood cell survival the addition of a minor traumatic disturbance or the creation of more turbulence would be expected further to increase the random destruction of red blood cells. If the trauma or turbulence were severe enough, red blood cell survival could be shortened to the point of hematologic decompensation with the production of anemia. Development of re-
gurgitation around the prosthetic valve would be expected to cause additional turbulence and red blood cell destruction. The two patients who were anemic following aortic valvular replacement had developed regurgitation around their prostheses. In case 2 the anemia was mild, and there was a grade-II immediate decrescendo diastolic murmur heard along the left sternal border. In case 38 the anemia was severe, and there was a grade-IV/VI murmur of aortic regurgitation. In both cases the Coombs antiglobulin test was negative.

From the limited data on patients with multiple valve replacement it appears that the red blood cell survival is slightly shortened. T/2 is similar in multivalvular replacement, aortic valve replacement, and aortic valve disease. It is interesting that the addition of a mitral or a mitral and tricuspid valve prostheses does not seem to decrease the red blood cell survival as compared with patients with an aortic prosthesis alone. The flow across the mitral and tricuspid prosthesis during diastole is at a lower pressure than the flow across the aortic prosthesis during systole. Accordingly, the turbulence produced by the mitral and tricuspid prostheses would be expected to be less than that produced by the aortic valve prosthesis. In other words, the turbulence produced by the rather low pressure systems of the tricuspid and mitral valve prostheses is probably not sufficient to add significantly to the rate of destruction of red blood cells. Investigations of the effects of mitral valve disease and mitral valve prostheses on red blood cell survival are underway.

Regurgitation around the mitral prosthesis occurs under high pressure during systole. This would be expected to increase intracardiac turbulence and shorten red blood cell survival. Patient 43 had a normally functioning aortic prosthesis. The results of cardiac catheterization were compatible with regurgitation around her mitral prosthesis. She had a shortened red blood cell survival of 18 days and mild hemolytic anemia. Patient 51 had a normally functioning mitral prosthesis but he had mild regurgitation around the aortic prosthesis. This patient had also been studied preoperatively. His postoperative survival was shorter than his preoperative survival. In the postoperative study the percentage of randomly destroyed red blood cells was found to be more than double the percentage of randomly destroyed red blood cells in the postoperative study. Although the number of patients studied before and after operation are small, the results suggest that the normally functioning aortic valve prosthesis produces less hemolysis than the pre-existing aortic valvular disease. If, however, the prosthesis is malfunctioning, there is more intracardiac turbulence and more hemolysis is produced than is produced in the preoperative patient.

When the patient's cells were transfused into a normal recipient approximately 10 per cent were rapidly destroyed but the remaining cells had a normal survival ($r_2 = 0.020$). This suggests that approximately 10 per cent of the transfused cells had been damaged by the turbulence of the patient's circulation but the remaining cells were undamaged and survived normally in the recipient. The elevated value for $r_2$ for the patient's cells in the patient indicates that damage continued during the whole period of the survival study. This is suggestive evidence for an extracorpuscular cause of red cell destruction.

The mechanism of the shortening of the red blood cell survival appeared to be variable. In some patients it was due to a large percentage of initial subpopulation of rapidly destroyed cells ($G_1$, $r_1$), in others to an accelerated rate of destruction of the principal cell population and in the remainder to a combination of these two mechanisms. There did not appear to be any correlation between the severity or nature of the valvular disturbance and the method involved in the red blood cell destruction.

In the multiple valve replacement group, patient 7 had a triple valve replacement complicated in the postoperative period by
the development of mitral and tricuspid regurgitation and a Coombs positive hemo-
lytic anemia. His hematocrit level was 25 per cent 3 months after surgery, when his red blood cell survival was found to be 16 days. This hematocrit value is lower than would be expected with a red blood cell survival of 16 days. This suggests that other factors, such as bone marrow depression, were probably operative in addition to me-
chanical and autoimmune hemolysis. At the time of reoperation the hematocrit value was normal and a Coombs test was negative. He was restudied 4 months after the second operation. At that time the red blood cell survival was in the usual range for patients with multiple valve prostheses. The me-
chanism of this patient's anemia is complicated by the addition of other factors, such as autoanti-
bodies and possible bone marrow depression in addition to mechanical hemolysis. The fact that the anemia was self-limited and re-
ponded to corticosteroids may indicate that the factors of bone marrow depression and the production of autoantibodies were more important in the etiology than the me-
chanical trauma to the erythrocytes.

There were two other patients who had positive Coombs tests. Case 36 had aortic valvular disease with value for T/2 of 25 days. Case 49 had a double valve replacement with a T/2 of 22 days. The mechanism for the de-
velopment of the autoantibody is not known. Positive Coombs tests have not been described previously as occurring spontaneously in pa-
tients with aortic valvular disease, but have been described following aortic valvular re-
placement.26 Perhaps there is a relationship between increased red blood cell destruction and the production of antigenic red blood cell fragments with the subsequent stimulation of autoantibodies to erythrocytes.

Summary

Red blood cell survival was determined in patients with aortic valvular disease, postop erative patients with aortic valvular ball-valve prostheses and postoperative patients with multiple ball-valve prostheses. The red blood cell survival was reduced in the majority of patients in each group when compared with the red blood cell survival from a nor-
mal control group.

A detailed analysis of the survival curves suggested that in many patients there was more than one population of red blood cells. The first population displayed rapid random destruction. This population was not present in normal persons in the control group. The second population showed the usual decline in radioactivity due to random destruction and loss of the red cell label due to elution. The shortened red blood cell survival in some pa-
tients was due to a large percentage of the first population of randomly destroyed red blood cells, in other patients to an accelerated rate of destruction of the usual single population of cells while others had a combination of the two mechanisms.

A mechanism of mechanical hemolysis due to increased intracardiac turbulence was sug-
gested as a cause for the shortened survival. When the turbulence was increased by a leak around the aortic or mitral valve prosthesis the red blood cell survival was found to be further decreased. In some cases this reduction in survival was enough to produce hemolytic anemia.

The Coombs antiglobulin test was positive in three patients. The suggestion was made that the development of autoantibodies to red blood cells was secondary to increased de-
struction of red blood cells.

Acknowledgment

The authors are grateful to Drs. R. Herr and C. W. McCord for their continued interest in this project; to Dr. D. A. Rigas who helped with the mathematical interpretation and computer analysis of the red cell survival curves throughout the study; to Dr. L. W. Ritzmann of the Veterans Administration Hospital for allowing us to study his patients and for performing duplicate red cell survival curves on some of our patients; to Dr. B. Pirofsky for performing the antiglobulin tests; to Drs. D. G. Kassebaum, F. E. Kloster, R. P. Lewis, G. A. Porter and the other members of the staff who acted as volunteers for the normal red cell survival studies; and finally, to Elma Lehto for her excellent secretarial assistance.

Circulation, Volume XXXII, October 1965
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Red Blood Cell Survival in Patients with Aortic Valvular Disease and Ball-Valve Prostheses

MICHAEL T. BRODEUR, DONALD W. SUTHERLAND, ROBERT D. KOLER, ALBERT STARR, JEAN A. KIMSEY and HERBERT E. GRISWOLD

_Circulation_. 1965;32:570-581
doi: 10.1161/01.CIR.32.4.570

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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