Renal Hemosiderosis in Patients with Prosthetic Aortic Valves

By William C. Roberts, M.D., and Andrew G. Morrow, M.D.

During recent years, considerable effort has been directed to the development of effective operative methods for the correction of stenotic and regurgitant malformations of the aortic valve. Initially, reconstructive procedures on the valve were performed, but the results of these operations were generally unsatisfactory. Prosthetic valves were then utilized, and the first ones to gain wide acceptance were constructed of flexible Teflon fabric, either as individual leaflets, or as tricuspid facsimiles of the normal aortic valve. Flexible Teflon prostheses were utilized at the National Heart Institute for aortic valve replacement between 1961 and 1963, and the early and late experiences with these patients have previously been summarized in detail. The initial function of the valves was gratifying, but after a number of months the cusps stiffened, calcified, and then tore or perforated, giving rise to severe aortic regurgitation. The incompetent Teflon valves not only caused serious hemodynamic disturbances, but a number of the patients also became anemic and evidenced severe intravascular hemolysis. Detailed clinical and laboratory studies of four such patients revealed that the principal hematological abnormality was mechanical destruction of erythrocytes. Each of these patients later died. The present report focuses attention on an unusual pathological finding in the kidneys of these four patients, and in three additional patients with incompetent prosthetic aortic valves.

Group Studied

The seven patients died 13% to 33 months following complete replacement of the aortic valve with Teflon prostheses (table 1), and their ages at death ranged from 26 to 51 years. Preoperatively, the major hemodynamic abnormality in three patients was aortic valvular stenosis, in two aortic regurgitation, and in the remaining two aortic stenosis and regurgitation were of similar severity. In addition, three patients also had anatomic evidence of mitral valve disease, which produced no detectable hemodynamic abnormality in two patients, but severe mitral stenosis necessitating mitral commissurotomy as well as aortic valve replacement in one (C.P.). In each patient both clinical and hemodynamic findings indicated that the Teflon aortic valve had been functioning improperly for several months, and at the time of death or reoperation six patients had severe aortic regurgitation and the seventh had aortic stenosis (91 mm Hg peak systolic pressure gradient between the brachial artery and the left ventricle) and moderate regurgitation.

Each of the seven patients was anemic, the hematocrit values immediately before death or reoperation ranging from 30 to 38% (average 33%). All had had normal hematocrit readings (average 46%) prior to the initial operation (table 1). Five of the patients died with the Teflon prosthesis in place; and two (C.L. and W.L.) died 3 and 12 months, respectively, after the Teflon valves, which had been inserted 9% and 21 months previously, had been replaced with caged-ball prostheses.

At necropsy in addition to the usual examinations, sections of kidney, liver, spleen, and the bone marrow from each patient were studied after they had been stained by Perls' ferrocyanide method.

Results

The prosthetic valve leaflets in each of the seven patients were found to be thickened
and partially calcified, with large tears or perforations through them (figs. 1 and 2). Also, in patient 1, in whom a congenitally bicuspid valve had been replaced with two Teflon leaflets, residual obstruction resulted from hypoplasia of the left ventricular outflow tract, aortic annulus, and ascending aorta, the so-called tunnel form of congenital aortic stenosis (fig. 3).

Sections of kidney in each patient disclosed large deposits of iron when stained by Perl's ferrocyanide reaction (fig. 4). The iron was most densely concentrated in the cells of the proximal convoluted tubules and in their lumina. Smaller particles of iron were frequently apparent in Bowman's space, in the epithelial cells of the glomerulus, and in the cells constituting Henle's loops. On histological examination, the amounts of iron in the renal sections were graded 1 to 4, and in four of the seven patients maximal quantities (grade 4) were judged to be present (table 1). No stainable iron was seen in the liver or spleen of any patient. The bone marrow in each of the patients showed erythroid hyperplasia, and every section revealed iron, either in normal or decreased concentration.

Comment
In each of the seven patients described, both clinical and hemodynamic examinations indicated gross malfunction of the flexible Teflon aortic valve and, in addition, every patient was anemic. In six patients severe aortic regurgitation resulted from perforations or tears in the leaflets, and in the other the valve was both stenotic and regurgitant. Focal areas of calcification also were apparent on the prosthetic leaflets, particularly at the margins of the perforations, where they were unusually sharp and irregular. Appropriate studies in four of the patients indicated that the anemia was hemolytic in type, as evidenced by elevated reticuloocyte and serum bilirubin values and decreased erythrocyte survival, and that the hemolysis was intra-

Table 1

Data on Seven Patients with Teflon Aortic Valves and Renal Hemosiderosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yr, sex</th>
<th>Time Teflon valve in patient, mo</th>
<th>Defects in Teflon valve at operation or autopsy</th>
<th>Hemodynamic derangement produced by Teflon valve</th>
<th>Pre-operative hematocrit, %</th>
<th>Post-operative hematocrit, %</th>
<th>Renal iron, gr 0-4+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. M.C.† A63-165</td>
<td>33 F</td>
<td>15 (Bahnson)</td>
<td>Stenotic tears</td>
<td>AS</td>
<td>44</td>
<td>30</td>
<td>++++</td>
</tr>
<tr>
<td>2. C.L. A63-170</td>
<td>26 M</td>
<td>9% (Bahnson)</td>
<td>Perforations</td>
<td>AI</td>
<td>48</td>
<td>38</td>
<td>++</td>
</tr>
<tr>
<td>3. W.C. A63-175</td>
<td>36 M</td>
<td>16 (Muller)</td>
<td>Perforations</td>
<td>AS</td>
<td>43</td>
<td>32</td>
<td>++++</td>
</tr>
<tr>
<td>4. F.R.† A64-10</td>
<td>39 M</td>
<td>26 (Muller)</td>
<td>Perforations</td>
<td>AI</td>
<td>44</td>
<td>36</td>
<td>++++</td>
</tr>
<tr>
<td>5. W.C. A64-17</td>
<td>35 M</td>
<td>19 (Muller)</td>
<td>Perforations</td>
<td>AI</td>
<td>48</td>
<td>34</td>
<td>+++</td>
</tr>
<tr>
<td>6. C.P.† A64-139</td>
<td>47 F</td>
<td>31 (Muller)</td>
<td>Perforations</td>
<td>AI</td>
<td>49</td>
<td>36</td>
<td>++++</td>
</tr>
<tr>
<td>7. W.L.† A64-189</td>
<td>51 M</td>
<td>21 (Muller)</td>
<td>Perforations</td>
<td>AI</td>
<td>43</td>
<td>30</td>
<td>++</td>
</tr>
</tbody>
</table>

*Hematocrit several days before death or before operative removal of Teflon valve.
†Results of Cr51 RBC survival time, serum iron, direct and indirect Coombs' tests, osmotic fragility, fecal urobilinogen excretion, and total serum bilirubin reported elsewhere.
‡Teflon valve replaced by Starr-Edwards (S-E) valve 3 and 12 months before death.

Abbreviations: AS = aortic stenosis; AI = aortic regurgitation.
Muller-type Teflon prosthesis which had been in place for 26 months in patient F. R. Upper left: Prosthesis as viewed from the left ventricular aspect. Upper right: From the aorta. Lower: Opened prosthesis showing perforations in each of the three cusps. The margins of the perforations are lined by calcium deposits.

vascular, as evidenced by hemoglobinemia and hemosiderinuria. Hemolytic anemia has been described after a variety of intracardiac operations, and some patients with calcific aortic valve disease have been shown to have chronic intravascular hemolysis or overt anemia before operation. The mechanism of erythrocyte destruction in all of these patients appears to be a mechanical one, the result of turbulent flow and shearing forces imparted

Figure 1

Muller-type Teflon prosthesis which had been in place for 26 months in patient F. R. Upper left: Prosthesis as viewed from the left ventricular aspect. Upper right: From the aorta. Lower: Opened prosthesis showing perforations in each of the three cusps. The margins of the perforations are lined by calcium deposits.

Figure 2

Opened Teflon aortic valvular prostheses of patients C. F. (upper) and W. L. (lower). The valve in the upper view had been in place for 31 months, and the one in the lower view, for 21 months.
RENAL HEMOSIDEROSIS

Figure 3

Bahnson-type Teflon aortic valve leaflets in patient M. C. The prosthesis was severely stenotic as well as allowing regurgitation. In addition, a small opening below the prosthesis led into a periaortic aneurysm. Blood apparently entered this aneurysm freely, since it contained no thrombus. The orifice of this aneurysm was located below the stenotic prosthetic aortic valve, and blood apparently circulated in the aneurysm at left ventricular pressure. The turbulence produced by this accessory exit for left ventricular outflow may have been a factor contributing to the hemolysis in this patient. A severe jet lesion may be seen in the ascending aorta in the lower photograph. A peak systolic pressure gradient of 91 mm Hg had been measured between the brachial artery and left ventricle in this patient 43 days before she died.

to the blood in an area where velocity and pressure are rapidly changing. In most patients, as in the present ones, valvular regurgitation has been a prominent feature, since regurgitant flow greatly increases the frequency with which the cells are traumatized.4, 6

Renal hemosiderosis is the anatomic indicator of intravascular hemolysis.15–21 Deposits of iron in the cells of the convoluted tubules have been described in association with most of the diseases characterized by intravascular hemolysis. The classic one is paroxysmal nocturnal hemoglobinuria,19, 20 but renal hemosiderosis has also been seen in patients with paroxysmal cold and march hemoglobinuria, thalassemia, hereditary spherocytosis, sickle cell disease, chronic auto-immune hemolytic anemia, transfusion reactions, and blackwater fever.18 Some of these conditions produce only acute episodes of hemolysis, and the quantity of stainable iron seen in the kidney is small. When hemolysis is chronic, however, the amount of iron which accumulates in the kidneys may be striking.

When an excessive amount of iron is liberated into the blood by intravascular hemolysis, it is deposited exclusively in the kidney and none is evident in the liver or spleen, except when multiple transfusions have been given.14, 18–21 This general distribution of iron was found in each of the seven patients described, and in their kidneys the iron was concentrated in the cells of the proximal convoluted tubules, although a few deposits were seen in the cells of Henle’s loops and in the epithelial cells lining Bowman’s space. In addition, iron was usually present in the lumina of the convoluted tubules and in Bowman’s spaces. An identical distribution of iron pigment in the kidneys has been observed in animals following intravenous injections of hemoglobin.16, 17, 21 There appear to be only two conditions in which iron is

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Figure 4

The kidney of patient C. P. Upper left: Not fixed, showing marked brown discoloration of the cortex. Upper middle: Same kidney following immersion in Perls' ferrocyanide solution.
deposited in only a single organ: one is intravascular hemolysis with renal hemosiderosis, and the other is idiopathic pulmonary hemosiderosis. The iron deposited in the renal tubules in the former condition gradually disappears if hemolysis ceases, but in pulmonary hemosiderosis the iron in the lung is contained in macrophages and persists indefinitely, apparently because the hemosiderin-laden macrophages are unable to gain access to the circulation.

The mechanisms by which iron is deposited in the kidneys with intravascular hemolysis have been greatly clarified by the observations of Laurell and Nyman\(^22\) and Lathem.\(^23\) When erythrocytes are destroyed, hemoglobin is liberated directly into the plasma, which contains the protein haptoglobin. Each molecule of haptoglobin (molecular weight = 178,000) binds and transports two molecules of free hemoglobin (molecular weight = 66,000). The molecular weight of the haptoglobin-hemoglobin complex (310,000) precludes renal excretion, and it is taken up by the reticuloendothelial cells of the liver, spleen, and bone marrow, and degraded so that the heme molecule is processed in the bilirubin-urobilinogen cycle. This normal mechanism for removing free hemoglobin from plasma has been variously referred to as the "reticuloendothelial," "intercellular," or "extracellular" process. In a normal individual, however, each 100 ml of plasma contains only sufficient haptoglobin to bind 100 to 140 mg of hemoglobin, and when the plasma hemoglobin concentration exceeds these levels, it cannot be bound in a protein complex, is filtered by the glomerulus, and is reabsorbed by the proximal convoluted tubules. Lathem has shown that the urinary excretion of free hemoglobin increases proportionally as the plasma level of free hemoglobin increases, but that the maximal rate of tubular reabsorption of free hemoglobin does not change with increasing loads, and averages approximately 0.58 mg/min/m\(^2\) of body surface.\(^23\) Whipple and associates\(^24\), \(^25\) injected solutions of hemoglobin intravenously into dogs and noted that initially the hemoglobin was rapidly taken up by the renal tubular cells; with repeated injections, however, the tubular cells apparently became saturated with hemoglobin, and thereafter most of the hemoglobin filtered by the glomeruli was excreted in the urine. The absorptive capacity of the proximal convoluted tubular cells appears to be an active one, according to Oliver and associates,\(^26\) who demonstrated that absorption of iron occurred only in viable tubules.

There are conflicting views concerning the effects of elevated plasma hemoglobin levels on renal function. Miller and McDonald,\(^27\) McDonald and associates,\(^28\) and DeMaria and Harris\(^29\) found that intravenous hemoglobin infusions produced renal vasoconstriction and led to a decrease in the glomerular filtration rate and effective renal plasma flow, and to an increase in tubular reabsorption. These effects were transient, however, and occurred only during the infusion; when the infusion was stopped these values promptly returned to normal although the concentration of free hemoglobin in the plasma remained elevated. The actual level of plasma hemoglobin in the studies appeared to be of less importance in causing acute changes in renal function than did the rate at which the level was achieved. These alterations in renal dynamics and urine flow could be reversed immediately by magnesium sulfate, a known vasodilator, or prevented if this drug was administered prior to the hemoglobin infusion.\(^29\)

In contrast to the findings in the acute experiments above, a number of studies in patients with various forms of hemoglobinuria for 30 seconds. The cortex is now blue indicating the presence of large quantities of iron. Upper right: Section of whole kidney stained by Perls' ferrocyanide solution. The iron deposits are located exclusively in the cortex. Lower left: Closer view of section of cortex. The surface of the kidney is at the top (x25). Lower right: Deposition of iron occurs predominantly in the cytoplasm of the proximal convoluted tubules, sparing entirely the distal convoluted tubules and usually also the glomeruli (x290).
have indicated that these diseases do not cause significant impairment of renal function.\(^4\), \(^14\), \(^18\), \(^19\), \(^30\)-\(^32\) In the seven patients of this series, detailed assessments of renal function were not made, but urinalyses and determinations of whole blood urea nitrogen were carried out in six of the patients several days before they either died of aortic regurgitation, or had a defective Teflon valve replaced. In four patients, urea nitrogen was normal, 12 to 16 mg/100 ml, and in the other two, the values were 22 and 23 mg/100 ml. No patient had proteinuria or casts; four had 1 to 8 leukocytes per high-power field on microscopic examination of the urinary sediment. These findings are comparable to those commonly noted in any patient with more or less severe congestive heart failure. On histological examination, the appearance of the kidneys of these patients was similar to that of the kidneys described by Havill and associates\(^33\) in dogs in which renal hemosiderosis had been induced by hemoglobin infusions; there was no apparent damage to the renal cells, and the lumina of the tubules were not obstructed by deposits of iron. The studies of Havill and associates indicated that deposits of iron in the convoluted tubules of the dog cause no injury or functional impairment in the kidney. Also, when their animals with renal hemosiderosis were given otherwise lethal doses of mercuric chloride, no renal damage occurred, apparently because the iron-laden cells in the proximal convoluted tubules could not absorb the mercury.\(^33\) The intracellular iron in the kidneys of these patients with hemosiderosis provoked no inflammatory or fibrous reaction in contrast to the striking fibroblastic or sclerotic reactions commonly observed with hemochromatosis. Finally, among the many reports concerning renal hemosiderosis, there are descriptions of only two patients in whom hemosiderosis was associated with anatomically diseased kidneys; in both patients renal damage may have resulted from other factors.\(^20\), \(^34\)

There is evidence that when intravascular hemolysis ceases, iron will disappear from renal tubular cells. Cappell\(^18\) and Whipple and associates\(^17\), \(^24\) noted this in mice and dogs when repeated intravenous injections of iron solutions were discontinued. The iron (stored as ferritin) may leave the tubular cells either via the urine, being secreted by the epithelial cells or contained within sloughed tubular cells, or via the blood, passing through the peritubular basement membrane into the peritubular capillaries.\(^19\) The clinical observation of persisting hemosiderinuria after the cessation of hemolysis strongly suggests that the urinary route of excretion of the iron is most important.\(^18\) Evidence that the blood route plays a significant role is scanty.\(^19\), \(^33\)

Two of the seven patients in this study had undergone replacement of incompetent Teflon aortic valves with competent Starr-Edwards prostheses 3 and 12 months, respectively, before death. Necropsy in each of these patients disclosed renal hemosiderosis, but the degree of iron deposition was less than in any of the other five patients. It is possible that the iron present at autopsy in the kidneys of these two patients had been deposited when incompetent Teflon prostheses were in place. On the other hand, the iron deposits may have resulted from continued, but less severe hemolysis caused by the caged-ball prostheses, since red cell survival has been shown to be decreased in certain patients with Starr-Edwards aortic valves.\(^9\), \(^10\), \(^12\) In addition to the two patients mentioned, we have examined the kidneys of one other patient who died 4 months following Starr-Edwards replacement of the aortic valve. The prosthetic valve was competent at autopsy, but large quantities of iron were present in his kidneys.

**Summary**

Seven patients with prosthetic aortic valves and anemia are described. In six, the Teflon valves had become incompetent as a result of perforations or tears in the prosthetic cusps, and in the seventh the valve was severely stenotic as well as regurgitant. The anemia in each patient was secondary to intravascular hemolysis resulting from damage to the erythrocytes traversing the malfunctioning valve. Severe renal hemosiderosis, the anatomic in-
indicator of severe intravascular hemolysis, was present in each patient. Although deposits of iron in the kidney in these circumstances may be extreme, no significant renal damage nor impairment of renal function appears to occur as a result of this deposition.

References


It Was an Essay That Decided Me

I was moved, rather, by a sort of curiosity, which was, however, directed more towards human concerns than towards natural objects; nor had I recognized the importance of observation as one of the best means of gratifying it. At the same time, the theories of Darwin, which were then of topical interest, strongly attracted me, for they held out hopes of an extraordinary advance in our understanding of the world; and it was hearing Goethe's beautiful essay on Nature read aloud at a popular lecture just before I left school that decided me to become a medical student.—Sigmund Freud. In Fabricant, N. D. (Editor): Why We Became Doctors. New York, Grune & Stratton, 1954, p. 43.
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