

Renal Haemosiderosis in Patients with Prosthetic Heart Valves

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SUMMARY

Renal haemosiderosis is the anatomical indicator of intravascular haemolysis. The incidence of renal haemosiderosis was studied in 66 patients with valve prostheses, 32 patients with advanced rheumatic-type valvular deformities and in 21 consecutive routine adult autopsy cases.

Significant renal haemosiderosis was present in 17 out of the 66 patients with prostheses. Mechanical factors may have been operative in 3 out of 5 patients with abundant renal iron. In 10 patients significant renal haemosiderosis was observed in the absence of any abnormality of the prosthesis. Siderosis was present in only 1 of 53 control subjects. Postmortem renal haemosiderosis may show clinically unapparent intravascular haemolysis. Although clinically apparent haemolysis occurs more often with the UCT aortic prosthesis than with the UCT mitral prosthesis, the latter has a higher frequency of unapparent intravascular haemolysis as revealed by renal haemosiderosis.

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Haemolytic anaemia associated with an intracardiac prosthetic valve was reported for the first time by Rose *et al.*¹ in 1954. This complication was confirmed experimentally in dogs by Stohman *et al.*² in 1956. While many subsequent reports dealing with the clinical and haematological aspects of haemolysis associated with intracardiac valve prostheses have been published,³⁻⁸ only two refer to associated renal haemosiderosis.^{9,10} Renal haemosiderosis is the anatomical indicator of intravascular haemolysis.⁹ When an excessive amount of iron is liberated into the blood by intravascular haemolysis, it is deposited exclusively in the kidney and none is evident in the liver or spleen, except when multiple transfusions have been given. Needle biopsy of the kidney has been used to diagnose renal haemosiderosis in the haemolytic anaemias.¹¹

From our institution, Schrire *et al.*¹² in 1970 reported the immediate and long-term results of aortic valve replacement with the University of Cape Town (UCT) aortic valve prosthesis. Haemolytic anaemia was only encountered with the cloth-covered valve. In a total series of 104 patients with cloth-covered aortic prostheses, haemolysis was present in 4, of whom 2 had aortic incompetence. Haemolytic anaemia was not an important problem in Schrire and Barnard's 122 patients with a UCT mitral prosthesis.¹³ One patient developed haemolytic anaemia when

mitral incompetence appeared. Another patient, with aortic and mitral valve replacements, developed intractable haemolytic anaemia which was cured only when the incompetent mitral valve was replaced.

Studies on patients with valvular heart disease,^{6,14-17} particularly aortic stenosis and incompetence, revealed the presence of intravascular haemolysis. Since the incidence of renal haemosiderosis in our patients with valve prostheses was unknown, it was decided to examine the incidence and severity of renal haemosiderosis in patients who came to autopsy with prosthetic heart valves, as well as in a group of patients with severe rheumatic-type valvular deformities and a routine autopsy control group. The iron content of 'normal' kidneys appears to have been neglected, and a recent histological and chemical study of tissue iron¹⁸ gives no information regarding the iron content of 'normal' kidneys.

PATIENTS AND METHODS

Sections of the kidneys were available from 66 patients with cloth-covered heart valve prostheses who were autopsied in the Department of Pathology, Groote Schuur Hospital and the University of Cape Town during the years 1963-1972. These 66 patients (Table I) comprised 25 patients with a UCT aortic valve prosthesis, 20 with a UCT mitral valve prosthesis and 12 patients with multiple prostheses. Nine patients with a Starr-Edwards mitral valve prosthesis were also studied. Two further groups of patients were studied as controls. Firstly, the kidneys of 32 patients who died with advanced chronic rheumatic-type valvular deformities were examined microscopically for haemosiderin. None of these 32 patients had a pros-

TABLE I. AUTOPSY INCIDENCE AND SEVERITY OF RENAL SIDEROSIS IN 66 PATIENTS WITH PROSTHETIC HEART VALVES

Type of prosthesis	Renal iron content			
	Nil	Scanty (+)	Significant siderosis	
			Moderate (++)	Abundant (+++)
UCT aortic	14	7	2	2
UCT mitral	5	9	5	1
Multiple prostheses ...	6	2	2	2
Starr-Edwards mitral ...	4	2	3	0
Number of cases ...	29	20	12	5

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thesis and most had died of cardiac failure. The second control group consisted of kidneys from 21 consecutive routine adult autopsies.

All sections of kidney were stained by the haematoxylin and eosin, periodic acid-Schiff methods and the amount of haemosiderin present was assessed on sections stained by Perls' Prussian blue method (Perls, 1867). Renal haemosiderosis was graded as follows: 0 — no iron present; + — scanty iron present; ++ — moderate amount of iron present; +++ — abundant iron present. For the purpose of this report the term 'significant haemosiderosis' refers to moderate or abundant iron deposition. Sections of liver and spleen in these 119 patients were also evaluated for the presence of iron. Local lesions (such as infarcts) were disregarded.

RESULTS

The incidence and severity of renal haemosiderosis at autopsy in the 66 patients with prosthetic heart valves is given in Table I.

Large amounts of iron (Fig. 1) were present in the kidneys of 5 of the 66 dying patients with valve prostheses. The haemosiderin granules were usually seen within the cells of the convoluted tubules (Fig. 2), but in some instances iron was also present in the epithelial cells of the glomeruli. This distribution is similar to that observed by Roberts and Morrow.⁹ No significant amount of iron was seen in the liver or spleen of any of these 66 patients. Table II gives details of the 5 patients with abundant

renal siderosis. The 2 patients with a UCT aortic prosthesis both survived one month after operation. One died of cardiac failure associated with florid, active rheumatic pancarditis and the other had a fungal infection of the prosthesis. The third patient (a 39-year-old female) had vegetations on the UCT aortic and mitral prostheses and culture grew *Candida parasilosis*. Death followed a cerebral embolus 6 months after operation. The patient with a UCT mitral prosthesis and abundant renal iron had a 0.2-cm endothelial-lined defect at the side of the prosthesis. Death due to a cerebral embolus occurred 11 months after operation. The defect would have caused minimal incompetence. At autopsy no thrombi were found on the prosthesis or in the heart. The fifth patient with large deposits of renal iron had UCT aortic, mitral and tricuspid prostheses which appeared normal at autopsy. Death, 2 years postoperatively, was due to bilateral lobar pneumonia. Her prothrombin index had been very low (less than 10%) and intrapulmonary haemorrhage was also present.

If the normal haematocrit for males is 39-54% and that for females 35-40%, then 3 of these 5 patients (Nos. 2, 4 and 5 in Table II) were anaemic shortly before death. Two of these anaemic patients had normal pre-operative haematocrits, while no pre-operative haematocrit was available in the third (patient 5). Patients 2 and 5 (Table II) had fragmented red cells in their peripheral smears 2 months postoperatively.

Moderate amounts of renal iron (Table I) were demonstrated in 12 of the 66 patients with prostheses. One patient was a 28-year-old female with a Starr-Edwards mitral prosthesis who died only 2 days after operation. It

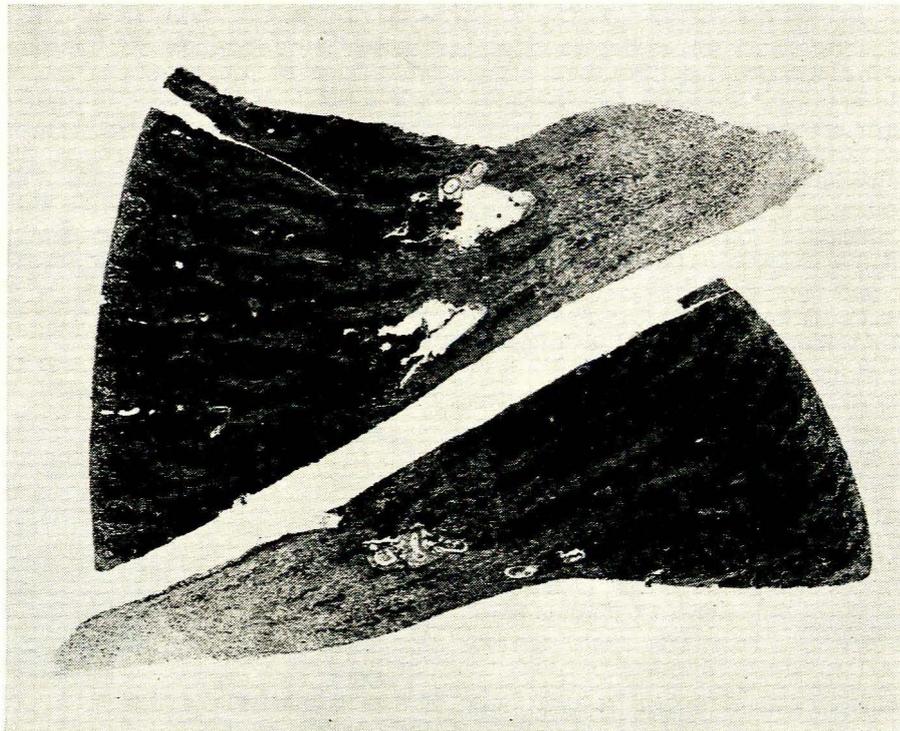


Fig. 1. Sections of the kidneys from patient 1 with a UCT aortic prosthesis. Abundant renal iron deposits in the cortex appear black (Perls' ferrocyanide reaction $\times 6$).

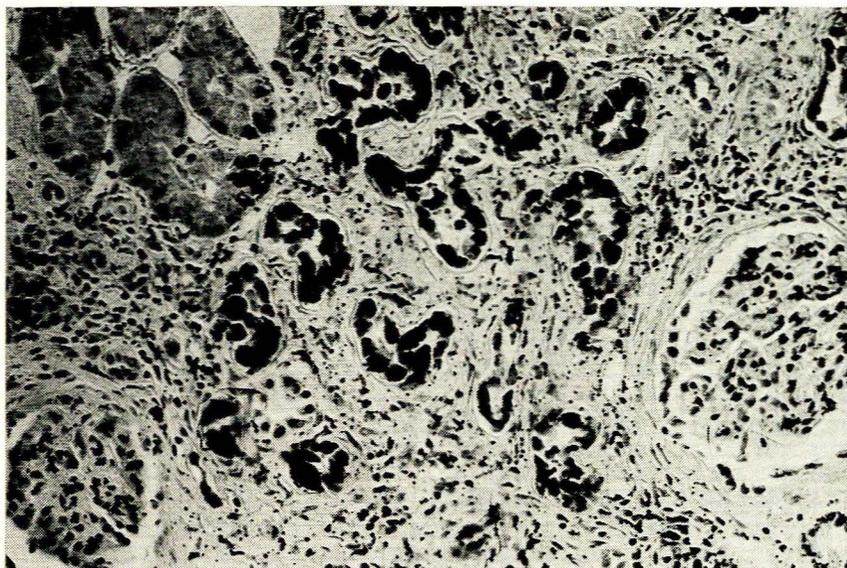


Fig. 2. Large dark-staining deposits of iron are present in the cytoplasm of the proximal convoluted tubules of patient 1 (Perls' ferrocyanide reaction $\times 160$).

TABLE II. DATA ON 5 PATIENTS WITH VALVE PROSTHESES AND ABUNDANT RENAL SIDEROSIS

Patient	Age (yrs)	Sex	Prosthesis present	Time prosthesis in patient (mo.)	Pre-operative haematocrit (%)	Late postoperative haematocrit (%)	Prosthesis at autopsy	Cause of death
1	20	F	UCT* aortic	1	38	35	Normal	Myocardial failure
2	48	M	UCT aortic	1	40	29	Fungal endocarditis	Cerebral infarct
3	39	F	UCT aortic, UCT mitral	6	43	38	Fungal endocarditis	Cerebral infarct
4	22	F	UCT mitral	11	46	27	Small defect side of ring	Cerebral infarct
5	43	F	UCT aortic, UCT mitral, UCT tricuspid	24	—	31	Normal	Pneumonia

* UCT = University of Cape Town.

is possible that her renal siderosis antedated the valve replacement operation. The other 11 patients had their prostheses from 1 to 48 months. With regard to these 11 patients with moderate renal siderosis, 2 had bacterial endocarditis, 3 had abundant thrombi preventing adequate closure of the prosthesis, and the other 6 had normal prostheses, but died of sudden cardiac arrhythmia (2), myocardial infarction (1), congestive cardiac failure (2) and following cholecystectomy (1).

Renal haemosiderosis was absent in 31 of the 32 control patients who died with advanced rheumatic-type valvular deformities (Table III). The only control patient showing renal siderosis was a 57-year-old White male who had mitral stenosis, trivial aortic stenosis and functional tricuspid incompetence. Cardiac symptoms had been present for 10 years. This same patient had large amounts of

iron in his liver and spleen as well, which suggested that his renal siderosis was part of a generalised haemosiderosis and not due to intravascular haemolysis. None of the 21 routine adult autopsy cases (Table III) showed renal siderosis.

TABLE III. AUTOPSY INCIDENCE OF RENAL SIDEROSIS IN 53 CONTROL PATIENTS

Valve lesion	Renal iron content	
	Nil	Scanty
Mitral stenosis/incompetence	25	1
Aortic stenosis/incompetence	6	0
Routine autopsy cases with no valve lesion	21	0

DISCUSSION

Significant (i.e. of moderate or severe degree) renal haemosiderosis was present in 17 of the 66 patients who died with valve prostheses. Mechanical factors may have been operative in 3 of the 5 patients who had abundant renal iron; 2 patients had infected thrombi preventing proper closure of their prosthesis and a third patient had a small defect at the side of the prosthesis between the cloth-covered metal ring and the mitral annulus. The remaining 2 patients with abundant renal iron had normal prostheses, as did 8 of the 12 patients with moderate renal iron. This is in keeping with the 2 cases of haemolytic anaemia reported by Schrire *et al.*¹² who had competent UCT aortic prostheses. The other 4 patients with moderate renal iron had extensive thrombi on the prosthesis (infected in 1 case), with resultant narrowing of the orifice of the prosthesis and valvular incompetence. Yacoub and Keeling³ reported that all their patients with a Starr-Edwards aortic valve prosthesis had shortened red cell lifespans. Those with competent valves had no anaemia but had compensated haemolytic states.

Thus in 10 patients significant renal haemosiderosis was observed in the absence of any abnormality of the prosthesis. All 7 of Roberts and Morrow's⁹ cases with renal haemosiderosis had malfunctioning Teflon aortic valves and haemolytic anaemia. Niles and Sandilands¹⁰ encountered renal haemosiderosis in 4 of 26 early deaths and 17 of 36 late deaths following heart valve replacement. The latter authors did not indicate the degree of the renal haemosiderosis nor did they specify the state of the prosthetic valves in such cases. Both groups of authors agree that renal haemosiderosis does not impair renal function. Crexells *et al.*,¹⁹ however, point out that the long-term effects of haemosiderinuria have not yet been adequately documented. Previous studies^{6,7,20} have revealed haemolysis in patients with prosthetic valves or heterograft valves with no evidence of incompetence. Davies²¹ stated that slight degrees of haemolysis are common with all mechanical valves.

The present study shows that postmortem renal haemosiderosis may show clinically unapparent intravascular haemolysis. In 6 of our patients with significant haemosiderosis, exuberant thrombi on the prosthetic valve ring, with resultant incompetence, may have been a factor in the genesis of the intravascular haemolysis.

Schrire *et al.*¹² reported significant haemolysis in 3,8% of patients with a UCT aortic valve prosthesis and Schrire and Barnard¹³ found haemolysis in 1,6% of their patients with a UCT mitral prosthesis (my percentages). The present autopsy study showed renal haemosiderosis in 44% of patients with a UCT aortic prosthesis and in 75% of patients with a UCT mitral prosthesis (average 60%). In the present series significant siderosis was present in 16% of patients with a UCT aortic prosthesis and in 30% with a UCT mitral prosthesis. These figures would appear to indicate that although clinically recognisable haemolysis is more often associated with an aortic valve prosthesis, subclinical intravascular haemolysis as indicated by renal siderosis is also common in patients with a UCT mitral prosthesis. Crexells *et al.*¹⁹ detected subclinical haemolysis in 67% of their 208 patients with valve prostheses.

The virtual absence of renal iron in the control subjects (Table III) with advanced rheumatic-type aortic and mitral valvular disease and in the routine adult autopsy patients, is evidence that the renal haemosiderosis in the patients with prostheses is due to the action of the prosthesis. It was first believed that the haemolysis in patients with prosthetic valves has a 'mechanical' or traumatic basis.² There is increasing evidence that the red cell damage may not result simply from the mechanical trauma of ball valve action on the red cells, but that haemodynamic disturbances, such as turbulent blood flow and shearing stress resulting from rapidly changing velocity and pressure, are the most important causes of traumatic mechanical damage.^{6,22,23} These factors and the interaction of red cells with the valve materials and with fibrin deposits around the valve, are probably all involved to some degree.²⁴

The degree of urinary iron loss from continued intravascular haemolysis may be severe and may even lead to chronic iron deficiency and superimposed iron deficiency anaemia.^{25,26} Much less common after valve replacement is haemolysis of the auto-immune type, with a positive antiglobulin test. The cause of this haemolysis is unknown.²⁷

The present study has shown that renal haemosiderosis occurs commonly in patients with normally functioning UCT aortic and mitral prostheses, as well as in patients with prostheses rendered incompetent by antemortem bland or infected thrombi. Detachment of the prosthesis with severe valvular regurgitation was not a significant problem in our patients.

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