SHORT COMMUNICATION

RENAL FUNCTION IN CHRONIC INTRAVASCULAR HAEMOLYSIS ASSOCIATED WITH PROSTHETIC CARDIAC VALVES

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SUMMARY

1. Glomerular filtration, water concentration and acid load tests, measurement of urinary protein and cell excretion rates, bacteriological examination of the urine, and analysis of the urinary amino acid content were carried out in eight patients with chronic intravascular haemolysis due to aortic valve replacement.

2. All results were normal except for a slight reduction in creatinine clearance rate in two patients and a slight elevation of urinary protein in a third; these abnormalities were considered of doubtful significance.

3. It is concluded that chronic intravascular haemolysis with its consequent renal haemosiderosis appears not to interfere with renal function.

Key words: renal function, haemolysis, artificial heart valves, haemosiderosis.

Intravascular haemolysis results in the release of haemoglobin into plasma, and that which is not bound to haptoglobin and albumin appears in the glomerular filtrate. From here a proportion is reabsorbed mainly by the proximal renal tubular cell and catabolized therein to haemosiderin, ferritin and other iron compounds which are subsequently released into the urine with cell sloughing and possibly by extrusion from the intact tubular cell (Hutt, Reger & Neustein, 1961; Roberts & Morrow, 1966; Sears, Anderson, Foy, Williams & Crosby, 1966). Usually little, if any, detectable free haemoglobin is found in the urine unless the haemolysis is severe (Ham, 1955; Andersen, Gabrieli & Zizzi, 1965; Andersen, Mouritzen & Gabrieli, 1966). Continuing chronic haemolysis of this type leads to heavy and selective deposition of iron in the kidneys (Leonardi & Ruol, 1960; Roberts & Morrow, 1966, 1969), and the urinary haemosiderin test is a sensitive indicator of this process (Slater & Fell, 1972). While available evidence suggests that renal haemosiderosis does not lead to severe structural or functional renal impairment there has been little detailed study of its effect upon renal function published. We report here an investigation of renal function in patients with chronic intravascular haemolysis due to aortic valve replacement.

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PATIENTS AND METHODS

Eight patients were investigated who had undergone aortic valve replacement with the Starr-Edwards prosthesis, Model No. 2300, 21–45 months previously. They all fulfilled the following criteria. They had evidence of chronic and continuing intravascular haemolysis with persistent gross haemosiderinuria for no less than the previous 1 year. There was no past history of renal disease, there had been no renal problems associated with the valve replacement operation, and there was no history or evidence of systemic disease. They were not in cardiac failure or hypertensive, had no severe anaemia, and were under good anticoagulant control with warfarin. Five were also taking oral iron but no other drugs, in particular no diuretics, were being given, and no patient was on a restricted sodium intake. A full explanation of the purpose and nature of all the proposed investigations was given to each of the patients and true consent for the study was obtained from them all.

Full haematological values were determined using the Coulter Counter Model ‘S’. Blood film examinations, reticulocyte counts and $^{51}$Cr-labelled erythrocyte survival studies were performed by standard methods (Dacie & Lewis, 1968). Plasma haptoglobin was estimated by an immunodiffusion technique (Partigen plates, Behringwerke AG; normal = 48–216 mg/100 ml), and serum lactic dehydrogenase was assayed on the LKB8600 reaction rate analyser at 37°C using the Boehringer test combination kit (normal = 116–467 i.u./l). In both cases precautions were taken to avoid in vitro haemolysis. Urine was examined for haemoglobin spectroscopically, and for haemosiderin as previously described (Slater & Fell, 1972).

Plasma urea and electrolytes were estimated by the Technicon auto-analyser. An endogenous creatinine clearance was performed using a 24 h urine collection with a mid-point blood sample. The serum and urine creatinines were estimated by the method of Hare (1950). Proteinuria was quantitated by the biuret method of Wootton (1964) on a 24 h urine collection. Urinary red and white cell excretion rates were measured by the method of Houghton & Pears (1957) using a 3 h urine collection. Quantitative urine cultures were done as described by McGeachie & Kennedy (1963). The presence or absence of glycosuria was determined using Labstix (Ames), and the amino acid content of the urine was analysed by colorimetry and paper chromatography (Rubinstein & Pryce, 1959; Parry, 1957). Renal concentrating power was assessed by measuring the urine osmolality with an Advanced osmometer after an 8 h period of dehydration. The short acid load test of Wrong & Davies (1959) was also carried out.

RESULTS

All renal tests were normal with three exceptions (see Table 1). Two patients (cases 1 and 6) had impaired creatinine clearances, and a third (case 2) had an elevated urinary protein level.

DISCUSSION

Renal haemosiderosis is a well-recognized feature of paroxysmal nocturnal haemoglobinuria (PNH) occurring with little or no demonstrable iron in the rest of the organs of the body unless multiple blood transfusions have been given (Dacie, 1967). This finding is not specific for PNH, however, and may be expected in any other condition in which there is chronic or recurrent intravascular haemolysis. Roberts & Morrow (1966, 1969) found renal haemosiderosis at post-mortem in patients with prosthetic heart valves, and it has been reported after other cardiac operations (Sigler, Forman, Zinkham & Neill, 1963; Liddy & Roberts, 1970) and in
TABLE 1. Renal investigations and haematological information in eight cases of aortic valve replacement. Haematological details

<table>
<thead>
<tr>
<th>Case</th>
<th>Known</th>
<th>Age and Time since duration of Hb (months)</th>
<th>PCV (%)</th>
<th>Retics (%)</th>
<th>Erythrocyte fragmentation</th>
<th>Plasma haptoglobin (mg/100 ml)</th>
<th>Serum lactic dehydrogenase (i.u./l)</th>
<th>Urinary haemoglobin ( ^{51} \text{Cr} ) erythrocyte survival ( t_{50} ) (days)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>49 M 30 17 15-3 45 2 - Nil 1000 Nil 22</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>48 M 21 18 12-1 36 3 ++ Nil 1520 Nil 20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>40 M 20 13-6 42 5 + Nil 800 Nil 19-5</td>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>4</td>
<td></td>
<td>41 M 22 13-0 39 4 ++ Nil 1200 Nil 14</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>39 M 21 11-3 32 4 + Nil 1920 Nil</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>53 M 21 13-4 39 2 ++ Nil 920 Nil 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>7</td>
<td></td>
<td>51 F 22 10-5 29 8 +++ Nil 1560 Nil 13-5</td>
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</tr>
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<td>8</td>
<td></td>
<td>49 M 15 12-2 34 6 +++ Nil 1800 Nil 11-5</td>
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* Results of \(^{51} \text{Cr}\)-labelled erythrocyte survival studies performed earlier (normal \( t_{50} = 25-33 \) days).

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TABLE 1 (continued). Renal investigations

<table>
<thead>
<tr>
<th>Case</th>
<th>Plasma urea (mg/100 ml)</th>
<th>Serum creatinine (mg/100 ml)</th>
<th>Creatinine clearance (ml min^-1 1-73 m^-2)</th>
<th>Proteinuria (g/24 h)</th>
<th>Urinary WBC excretion (cells/\mu l)</th>
<th>Urinary RBC excretion (cells/\mu l)</th>
<th>Urine osmolality post-dehydration (mosmol/kg)</th>
<th>Urine pH</th>
<th>Lowest urinary pCO_2 (mm Hg)</th>
<th>Highest titratable acidity (\muEq/min)</th>
<th>Highest ammonium excretion (\muEq/min)</th>
<th>Total hydrogen in excretion (\muEq/min)</th>
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<td>Nil</td>
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<td>Nil</td>
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<td>5-00</td>
<td>36-0</td>
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</table>

Normal values

Normal values: Not > 40 Not > 1-2 Not < 80 0-0-10 0-400000 0-200000 — Nil Normal See text 4-60- 5-24 24-51 33-75 60-124
unoperated calcific aortic valve disease (Roberts, 1966). Renal biopsy and post-mortem studies of affected kidneys (Leonardi & Ruol, 1960; Hutt et al., 1961; Roberts & Morrow, 1966, 1969) have shown that the haemosiderin deposits are most abundant in the cells of the proximal convoluted tubules, less pronounced in the loops of Henle, and only occasionally and scantly present in the cells of the distal tubules and in the interstitial tissue. No evidence of significant fibrosis or tubular atrophy was found in these studies. Experience mainly with cases of PNH suggests there is seldom, if ever, any serious or even significant renal functional impairment (Stats, Wasserman & Rosenthal, 1948; Crosby, 1953; Roberts & Morrow, 1966; Dacie, 1967). However, formal investigations of renal function in patients with chronic intravascular haemolysis (Bradley & Bradley, 1947; Leonardi & Ruol, 1960; Hutt et al., 1961), have been limited in extent, often confined to isolated cases, and altogether appear inconclusive. Further, in the occasional cases of renal failure considered likely to be directly related to renal haemosiderosis (Sussman & Kayden, 1948; Heitzman, Campbell & Stefanini, 1953; Blaisdell, Priest & Beutler, 1958) there have been other complicating pathological factors.

Prosthetic cardiac valves, particularly aortic valve replacements, are probably now the commonest cause of chronic intravascular haemolysis. All of the patients in this study were known to have gross haemosiderinuria for 15–22 months on repeated testing of their urine, often to the extent that the blue of the positive iron stain was visible on naked-eye inspection of the slide. Red cell fragmentation was repeatedly seen in all but one patient, and ⁵¹Cr-labelled erythrocyte survival studies performed early in these observation periods showed reduced erythrocyte survival. Current investigations demonstrated elevated serum lactic dehydrogenase and zero plasma haptoglobin levels in every patient indicating active haemolysis. These findings taken together confirm that significant intravascular haemolysis was occurring at the time of this study of renal function and had been in operation for at least 15–22 months. This strongly suggests that an appreciable degree of renal haemosiderosis has been present in these patients for equal periods of time. In this group as a whole no evidence of impairment of either glomerular or tubular function has been detected. The reduction in creatinine clearance found in two patients was slight as was the elevation in urinary protein in a third patient, and we consider these abnormalities to be of doubtful significance. Only a single measurement of creatinine clearance was made in each patient as experiments in this laboratory have shown a good reproducibility for clearances above 60 ml/min, the coefficient of variation being approximately 5%, and a good correlation with inulin clearance. The 8 h period of dehydration was also found to constitute a very adequate stimulus in these patients, the urine being concentrated to a mean (±SD) of 890±78 mosmol/kg which is three times the osmolality of plasma (285–290), and a U/P mosmol/kg ratio greater than 2 is usually taken as indicating normal renal concentrating ability.

In conclusion, these studies support the view that chronic intravascular haemolysis with renal haemosiderosis does not interfere with renal function.

ACKNOWLEDGMENTS

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REFERENCES


