Renal function and urate metabolism in late survivors with cyanotic congenital heart disease

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ABSTRACT Diminished glomerular filtration rate, proteinuria, and large hypercellular congested glomeruli with segmental sclerosis are found in late survivors with cyanotic congenital heart disease (CCHD). Hyperuricemia is common, acute gouty arthritis is less common than uric acid levels would predict, and overt tophaceous deposits of uric acid are exceptional. The role of the kidney in causing the basic biochemical disturbances, and the relative importance of impaired urate excretion vs urate overproduction have not been established. Accordingly, we reviewed the courses of two index patients and prospectively studied eight additional CCHD patients from 28 years to 46 years old with mean hematocrits of (62 ± 10%). Plasma creatinine concentration was normal (0.9 ± 0.1 mg/dl) yet glomerular filtration rate was mildly reduced to 93 ± 14 ml/min as measured by creatinine clearance and to 81 ± 6 ml/min as measured by 111In DTPA. Three patients had significant proteinuria and one was nephrotic. Plasma uric acid concentration was high in all but one (8.2 ± 2.1 mg/dl), mean 24 hr uric acid excretion was normal (564 ± 221 mg), and fractional uric acid excretion was relatively low (6.3 ± 2.6%). The two patients with highest plasma uric acid levels (12.0 and 10.2 mg/dl) had the lowest fractional excretions (2.8% and 4.0%). Both of these patients had diminished capacity to excrete a water load (38% and 27%/4 hr) and to maximally concentrate urine (520 and 635 mOsm/kg after water deprivation and vasopressin). In conclusion, high plasma uric acid levels in late survivors with CCHD are secondary to inappropriately low fractional uric acid excretion, not to urate overproduction. Hyperuricemia serves as a marker of abnormal intrarenal hemodynamics. Enhanced urate reabsorption appears to result from renal hypoperfusion reinforced by a high filtration fraction.


DIMINISHED glomerular filtration rates (GFRs) and proteinuria occur in late survivors with cyanotic congenital heart disease (CCHD).1-3 Histologic studies reveal large hypercellular, congested glomeruli with segmental sclerosis.4 Hyperuricemia is common, but acute gouty arthritis is less prevalent than uric acid levels would predict, and overt tophaceous deposits of uric acid are exceptional.5-6 The role played by the kidney in causing the basic biochemical disturbances is ill defined. Early studies incompletely assessed glomerular and tubular function or failed to exclude patients with congestive heart failure or receiving diuretics, which have potentially complicating effects. Our interest in renal function and uric acid was prompted by two patients who developed profound abnormalities of urate metabolism. We then prospectively studied eight additional adults with CCHD (table 1) to clarify the cause of diminished GFRs and to examine maximum urine dilution and concentration and renal tubular handling of uric acid.

Patients and methods

Patient 1. This patient was a 30-year-old man with levocardia in situs inversus, univentricular heart, and pulmonic stenosis. At age 31 years he experienced gouty arthritis in the hands and feet. On variable doses of diuretics but without a high purine diet, plasma uric acid concentration was 10.8 mg/dl. Plasma creatinine concentration was 1.0 mg/dl. Urinalysis was normal except for 2+ to 4+ proteinuria. Painless white ulcerating deposits on the pads of the fingertips were recognized as tophi (figure 1). By age 32 years increased symptoms prompted reevaluation of this patient, which established the cardiac diagnosis. Erythrocytosis necessitated intermittent phlebotomies. After undergoing a modified Fontan procedure7 the patient had resolution of erythrocytosis (postoperative hematocrit 37%) and appreciably improved exercise tolerance. Plasma uric acid concentration (off diuretics) was 6.4 mg/dl, serum albumin was 3.0 mg/dl, and plasma creatinine was 1.1 mg/dl. Proteinuria was 2.9 g/24 hr. At age 34 years, blood pressure increased to

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TABLE 1
Clinical characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Cardiac diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index patient 1</td>
<td>30</td>
<td>M</td>
<td>Single ventricle, pulmonic stenosis</td>
</tr>
<tr>
<td>Index patient 2</td>
<td>36</td>
<td>F</td>
<td>Eisenmenger’s complex</td>
</tr>
<tr>
<td>Prospective patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>44</td>
<td>M</td>
<td>Fallot’s tetralogy, Blalock shunt, PVD</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>F</td>
<td>Secundum atrial septal defect, PVD</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>M</td>
<td>Fallot’s tetralogy, Potts shunt, PVD</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>M</td>
<td>Single ventricle, PVD</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>F</td>
<td>Secundum atrial septal defect, PVD</td>
</tr>
<tr>
<td>6</td>
<td>33</td>
<td>M</td>
<td>Fallot’s tetralogy, pulmonary atresia</td>
</tr>
<tr>
<td>7</td>
<td>47</td>
<td>M</td>
<td>l-Transposition of great arteries, pulmonic stenosis, ventricular septal defect</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>M</td>
<td>Truncus arteriosus type I, PVD</td>
</tr>
</tbody>
</table>

PVD = pulmonary vascular disease.

140/105 mm Hg. Hematocrit was 48%, plasma uric acid concentration was 8.8 mg/dl, albumin was 4.0 mg/dl, and plasma creatinine was 1.2 mg/dl. Urinalysis disclosed 4+ proteinuria and occasional granular casts. Creatinine clearance was 61 ml/min/1.73 m². Twenty-four hour urine protein was 3.5 g and uric acid was 250 mg. Antinuclear antibody was negative and C₃, C₄, and CH₁₀₀ were within normal limits. Chronic joint pain persisted with exacerbation of gout in the feet. Allopurinol was administered without resolution of the tophi.

Patient 2. This patient was a 36-year-old woman with Eisenmenger’s complex. She presented with moderate pain in hands and elbows and episodes of acute gouty arthritis. Hematocrit was 51.3% and hemoglobin was 14.1 g/dl after repeated phlebotomies were performed at other institutions. Plasma uric acid concentration was 14 mg/dl or greater. Allergic reactions precluded administration of allopurinol. At age 45 years she experienced rapidly progressive right ventricular failure prompting vigorous diuresis. Despite a low purine diet and administration of probenecid, plasma uric acid concentration was 17 mg/dl. Hyperuricemia was considered secondary to inadequate renal excretion (440 mg/24 hr), with moderate renal insufficiency limiting the effectiveness of probenecid. Because of increasing gout of the elbows, metacarpal joints, and ankles, she was admitted to the hospital for allopurinal desensitization. Evaluation revealed a plasma creatinine of 1.7 mg/dl with creatinine clearance of 27 ml/min/1.73 m² and GFRs by ¹¹¹In DTPA clearance of 24 ml/min/1.73 m². Urinalysis was normal except for 3+ proteinuria. Several 24 hr urine samples contained an average 3 g of protein, less than 10 meq of sodium, and 7 mg of calcium. Serum albumin concentration was 3.7 mg/dl. When probenecid was discontinued, uric acid excretion fell to 141 mg/24 hr and plasma uric acid rose to 24 mg/dl. Desensitization to allopurinol was unsuccessful: fever, rash, and thrombocytopenia developed within 2 days of commencing a 50 mg dose of the drug. Sulfinpyrazone, 100 mg bid, was used instead. Uric acid excretion rose to 632 mg/24 hr, and the plasma level decreased to 12.7 mg/dl.

Procedures. The study comprised 10 patients, the two index patients and eight in whom prospective studies were carried out (table 1). The eight subjects for the prospective study were drawn from the UCLA Adult Congenital Heart Disease Program. Six were men and two were women and their ages ranged from 28 to 47 years (table 1). All were outpatients without known intrinsic renal disease or clinically overt heart failure. Subjects were not under treatment for gout and none were taking diuretics, aspirin, or nonsteroidal anti-inflammatory agents. Informed consent was obtained as approved by the UCLA Human

FIGURE 1. Urate deposits (arrows) on the pads of a finger and thumb.
Subjects Protection Committee. All studies were performed during admission to the UCLA Clinical Research Center.

Blood samples and 24 hr urine specimens were analyzed for creatinine, uric acid, sodium, and protein. At 10 A.M. a standard oral water load of 20 ml/kg was administered. Urine was collected at two hr intervals for determination of creatine, sodium, uric acid, and osmolality. Blood specimens were obtained at the midpoints of these intervals for determination of creatinine, sodium, and uric acid. At 3 p.m. GFR was determined by \( ^{111}\mathrm{In}\ DTPA \) clearance after a 500 \( \mu \)Ci bolus injection, and blood samples were drawn 2, 3, and 4 hr later. Water deprivation was begun at approximately 7 p.m. If urine osmolality 10 hr later was less than 500 mOsm/kg, 5 units of aqueous vasopressin was administered subcutaneously and urine osmolality was measured 30 and 60 min later.

**Results (table 2)**

Mean hematocrits were 62 \( \pm \) 10%. Plasma creatinine was within normal limits (0.9 \( \pm \) 0.1 mg/dl), but GFR was mildly reduced as assessed by both creatinine clearance (93 \( \pm \) 14 ml/min) and \( ^{111}\mathrm{In}\ DTPA \) clearance (81 \( \pm \) 6 ml/min normalized to 1.73 m\(^2\)).

Plasma uric acid concentration was normal in only one subject. For the group, plasma uric acid concentration was elevated (8.2 \( \pm \) 2.1 mg/dl), uric acid excretion was normal (564 \( \pm \) 221 mg/24 hr), and fractional uric acid excretion was low (6.3 \( \pm \) 2.6%) relative to the high plasma level. The normal value for fractional uric acid excretion in gouty subjects has been reported to be 7.6 \( \pm \) 2.4%. There was a highly significant negative correlation between serum uric acid levels and fractional excretion of uric acid (r = -.82). Review of patient records revealed that plasma uric acid levels were uniformly stable at the time of study, i.e., within 1 mg% of levels recorded for up to 2 years before our investigation. The two patients with the highest plasma uric acid levels (12.0 and 10.2 mg/dl) had the lowest fractional excretion (2.8% and 4.0%, respectively). These two patients were the only ones with diminished capacity to excrete a water load (38% and 27%/4 hr) and to concentrate urine maximally (520 and 635 mOsm/kg after water deprivation and vasopressin). Proteinuria ranged from 0.19 to 7.96 g/24 hr and did not correlate with the degree of erythrocytosis (r = .35).

**Discussion**

Previous studies of renal abnormalities in patients with CCHD have focused on intrarenal hemodynamics or data obtained at autopsy. Findings included proteinuria, increased renal blood flow, increased renal vascular resistance, decreased renal plasma flow, normal or reduced GFRs, and histologic changes on biopsy or at autopsy. The meaning of published results remains unclear because of the diverse patient populations studied and because of the variation in clinical presentations and therapy. Many patients were receiving diuretics and some had infective endocarditis. These concerns were partially resolved by studies of the independent effects of erythrocytosis or heart failure in patients with normal hematocrits. In each category, intrarenal changes were similar to those in patients with CCHD, suggesting that high efferent glomerular arteriolar resistance — caused by the high blood viscosity of erythrocytosis or by angiotensin II and prostaglandins in heart failure — increases hy-

**TABLE 2**

<table>
<thead>
<tr>
<th>Laboratory characteristics</th>
<th>Water excretion (%)/4 hr</th>
<th></th>
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<tbody>
<tr>
<td>Patient No.</td>
<td>Hct (%)</td>
<td>Cr C (ml/min)</td>
</tr>
<tr>
<td>----------------</td>
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<tr>
<td>Prospective patients</td>
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<td>Mean</td>
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<tr>
<td>± SD</td>
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<tr>
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<tr>
<td>1</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>51.3</td>
<td>17</td>
</tr>
</tbody>
</table>

Cr C = creatinine clearance/1.73 m\(^2\); C DTPA = \( ^{111}\mathrm{In}\ DTPA \) clearance/1.73 m\(^2\); P uric = plasma uric acid; U uric = urine uric acid; FE uric = fractional excretion of uric acid; U protein = urine protein; NA = not available.
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draulic pressure across the glomerulus, augmenting the filtration fraction.

Increased filtration fraction, while tending to maintain GFR, elevates the oncotic pressure in postglomerular vessels perfusing the proximal tubules, promoting increased fluid and solute resorption and contributing to fluid retention. Isovolumetic phlebotomy in dogs produced a fall in filtration fraction and a natriuresis. Phlebotomy in patients with cor pulmonale reportedly increased renal plasma flow and decreased filtration fraction, with both changes correlating with diuresis. In one patient with CCHD and the nephrotic syndrome, isovolumetric phlebotomy was associated with similar changes in renal plasma flow and filtration fraction but with diminished proteinuria.

Renal histology (biopsy or autopsy) is characterized by enlarged congested glomeruli with basement membrane thickening, mesangial hypercellularity, and sclerosis as well as hyalination of afferent and efferent arterioles. DeJong et al. hypothesized that the high glomerular hydrostatic pressure caused capillary dilatation and initiated glomerular sclerosis. Glomerular sclerosis in turn served to reinforce hyperperfusion of remaining glomerular capillaries, augmenting the cycle of injury and leading to progressive renal failure. Phlebotomy might decrease the proteinuria by lowering transglomerular pressure gradients. Gowenstine et al. showed that both polycythemia vera without heart disease and erythrocytosis from intrinsic lung disease were associated with glomerular lesions similar if not identical to those described above. Our patients had mildly reduced GFRs as reflected in both creatinine and noncreatinine (In DTPA) methods of determination. None underwent renal biopsy, so we could not correlate our clinical observations with glomerular histology. The presence of proteinuria, however, implies intrinsic renal damage and is a typical manifestation of glomerular sclerosis. Mace et al. reported hyperuricemia with normal glomerular filtration in juvenile patients with cyanotic heart disease, an observation that underscored the slowly progressive nature of renal dysfunction. Occult soft-tissue visceral urate deposits, manifested overtly in the fingertips of our first index patient (figure 1), might contribute to renal dysfunction.

Studies of renal pathology do not suggest structural extraglomerular/vascular disease, but clinical reports point to abnormal renal tubular clearance of uric acid. Young and Mark followed 57 patients with Eisenmenger’s reaction to a mean age of 26 years. Seven patients (including two children) were hyperuricemic. Two had gouty arthritis (and normal renal function), an incidence of 5% compared with 0.3% in the general population. The incidence of acute gouty arthritis in patients with CCHD and hyperuricemia appears to be lower than in those with hereditary gout with equivalent elevations of uric acid. In one group of patients over 16 years of age, hyperuricemia was observed only when the hemoglobin concentration was increased by at least 130%. Gout occurred in 2% of these subjects, most of whom had 1+ to 2+ albuminuria and on renal biopsy glomerular but not tubular damage. Neither of the above reports resolved the relative importance of urate overproduction secondary to increased red blood cell turnover vs inadequate urate excretion. Increased turnover of nucleic acids was suggested by enhanced incorporation of nitrogen from dietary glycin-N into uric acid.

Passwell et al. studied renal tubular function in 21 children with CCHD, none of whom had albuminuria. Lack of aminoaciduria or glucosuria argued against proximal tubular dysfunction. Fractional excretion of uric acid was 15%, but plasma levels were not mentioned. Mace et al. reported reduced uric acid clearance in infants and young children with cyanotic heart disease. In our study of late survivors, high plasma uric acid levels were secondary to inappropriately low fractional uric acid excretion, not to urate overproduction. Importantly, the two patients with highest plasma uric acid levels and lowest fractional excretion had very high hematocrits. Enhanced urate resorption may result from renal hypoperfusion reinforced by a high filtration fraction. The inability of our patients to excrete a water load suggests hypoperfusion with increased resorption of fluid and urate from proximal tubules. Hyperuricemia serves as a marker of abnormal intrarenal hemodynamics in adults with CCHD.

References


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