Plasma and Urinary Cytokine Homeostasis and Renal Dysfunction during Cardiac Surgery

Sheena M. C. Gormley, F.C.A.R.C.S.I.,* William T. McBride, M.D.,† Marilyn A. Armstrong, Ph.D.,‡
Ian S. Young, M.D.,§ Elizabeth McClean, M.R.C.Path.,‖ Simon W. MacGowan, F.R.C.S.,#
Gianfranco Campalani, M.D.,# Terence J. McMurray, M.D.**

Background: Cardiac surgery induces changes in plasma cytokines. Proinflammatory cytokines have been associated with a number of renal diseases. The proinflammatory cytokines interleukin 8 (IL-8), tumor necrosis factor α (TNFα), and interleukin 1β (IL-1β) are smaller than the antiinflammatory cytokines interleukin 10 (IL-10), interleukin 1 receptor antagonist (IL-1ra), and TNF soluble receptor 2 (TNFsr2), and thus undergo glomerular filtration more readily. Accordingly, this study investigated the relation between plasma and urinary cytokines and proximal renal dysfunction during cardiac surgery.

Methods: Twenty patients undergoing coronary artery bypass grafting with cardiopulmonary bypass (CPB) were studied. Blood and urine samples were analyzed for proinflammatory and antiinflammatory cytokines. Proximal tubular dysfunction was measured using urinary N-acetyl-β-D-glucosaminidase (NAG)/creatinine and α_1-microglobulin/creatinine ratios.

Results: Plasma IL-8, IL-10, IL-1ra, and TNFsr2 values were significantly elevated compared with baseline. Urinary IL-1ra and TNFsr2 were significantly elevated. Urinary NAG/creatinine and α_1-microglobulin/creatinine ratios were also elevated. Plasma TNFα at 2 h correlated with urinary NAG/creatinine ratio at 2 and 6 h ($P < 0.05$) and with urinary IL-1ra at 2 h ($P < 0.05$). Plasma IL-8 at 2 h correlated with NAG/creatinine at 6 h ($P < 0.05$). Urinary IL-1ra correlated with urinary NAG/creatinine ratio after cross-clamp release and 2 and 6 h after CPB ($P < 0.05$).

Conclusions: Cardiac surgery using CPB leads to changes in plasma and urinary cytokine homeostasis that correlate with renal proximal tubular dysfunction. This dysfunction may be related to the renal filtration of proinflammatory mediators. Renal autoprotective mechanisms may involve the intrarenal generation of antiinflammatory cytokines. (Key words: Cardiopulmonary bypass; proximal tubule.)

CLINICALLY significant renal dysfunction after cardiac

⬦ This article is highlighted in "This Month in Anesthesiology." Please see this issue of Anesthesiology, page 5A.

---

surgery, as evidenced by elevated plasma urea and creatinine concentrations and decreased creatinine clearance, is uncommon.[1–4] Subclinical renal dysfunction, as measured using various markers of renal tubular damage, has been described in patients after cardiac surgery involving cardiopulmonary bypass (CPB) in the absence of overt changes in plasma urea and creatinine concentrations and creatinine clearance.[5,6] However, Jorres *et al.* showed that, in patients who developed an elevated plasma creatinine concentration after cardiac surgery, urinary N-acetyl-β-D-glucosaminidase (NAG) levels correlated with the increased creatinine.[5] The NAG/creatinine ratio is a sensitive and specific marker of renal tubular dysfunction.[6–8] NAG is a specific proximal tubular lysosomal enzyme that has a large molecular weight that prevents filtration at the glomerulus and is neither absorbed nor secreted by the tubules. Hence, any increase in the urinary concentration of NAG may be considered a result of tubular cell damage. It is conventional to express NAG as a ratio of urinary creatinine to minimize error caused by dilutional or concentrational effects.[5,9] Another marker of renal tubular dysfunction is α_1-microglobulin, which is filtered at the glomerulus and 95% reabsorbed at the proximal tubule; thus, any increase in urinary concentration would suggest proximal tubular dysfunction.[10,11] A greater knowledge of renal tubular dysfunction may lead to a greater understanding and subsequent prevention of clinically significant renal dysfunction.

Renal tubular dysfunction after cardiac surgery has been attributed to hypotension, reperfusion injury, and CPB-induced hemolysis.[12] However, these mechanisms alone do not explain subclinical or clinical renal dysfunction because these may occur in patients who did not sustain a perioperative hypotensive episode or who have not undergone CPB.[13,14] The kidney plays an important role in controlling the perioperative inflammatory cytokine response. Plasma proinflammatory cytokines—interleukin 1β (IL-1β), tumor necrosis factor α (TNFα), and interleukin 8 (IL-8)—have a low molecular weight (< 20 kd) and undergo glomerular filtration followed by denaturation by the proximal tubular cells.[15–17] In plasma, the inflammatory actions of proinflammatory cytokines are controlled in part by plasma antiinflammatory cytokines, interleukin 10 (IL-10), interleukin 1 receptor antagonist (IL-1ra), and tumor necrosis factor soluble receptor 2 (TNFsr2).[18] However antiinflammatory cytokines are of greater molecular weight than proinflammatory cytokines (> 20 kd) and thus less

readily filtered by the glomerulus. The proximal tubules therefore cannot fully rely on filtered plasma antiinflammatory cytokines to limit the potential cytotoxic effects of the filtered proinflammatory cytokines. TNFα has been associated with a variety of renal diseases, and the role of TNFα in mediating renal insufficiency after CPB has been suggested but not fully investigated.[19,20] Proinflammatory cytokines lead to the production of nitric oxide *via* inducible nitric oxide synthase (iNOS) in cell culture, suggesting a direct mechanism for cell damage.[21,22]

The aim of this study was to investigate how elements of the proinflammatory and antiinflammatory response previously identified during cardiac surgery may be linked to perioperative renal dysfunction.[23] We wished to determine whether there was a correlation between the magnitude of the plasma proinflammatory response and perioperative proximal tubular damage as measured by urinary NAG/creatinine and α_1-microglobulin/creatinine ratios. Changes in urinary proinflammatory and antiinflammatory cytokines had not been investigated previously in patients undergoing cardiac surgery. We investigated if the renal tract was itself capable of generating a protective antiinflammatory cytokine response during the period of renal handling of filtered proinflammatory cytokines.

Methods

After obtaining Research Ethics Committee approval and informed written consent, 20 American Society of Anesthesiologists grade III–IV patients undergoing elective coronary artery revascularization grafting using CPB were enrolled into the study. All patients were receiving triple therapy with β blockers, nitrates, and calcium antagonists. Exclusion criteria were unstable angina, myocardial infarction within the previous 3 months, diabetes, heart or liver failure, and documented renal dysfunction as indicated by an elevated plasma creatinine concentration. These exclusion criteria were applied to minimize interpatient variability and to provide a group of patients at low risk of developing postoperative renal failure. All patients received benzodiazepine or benzodiazepine–opioid premedication and had a pulmonary artery flotation catheter placed from which blood samples were taken. Patients were anesthetized with fentanyl 20–25 μg/kg, pancuronium 100–150 μg/kg, and anesthesia was maintained using target controlled intravenous anesthesia with propofol (target concentration, 0.5–4.0 μg/ml) and fentanyl increments. Mean arterial pressure during CPB was maintained above 50 mmHg.

Blood samples were obtained at baseline (before induction of anesthesia, sample 0), after aortic cross-clamp release (sample 1), and 2 and 24 h after the termination

Table 1. Demographic and Perioperative Data

Male:Female	19:1
Age (yr)	60 ± 7
Weight (kg)	80.7 ± 9.3
CPB time (min)	89.7 ± 19.3
Cross-clamp time (min)	52.0 ± 11.4
Number of grafts	3.2 ± 0.8
Time to extubation (h)	20.7 ± 6.6

Values given are mean ± SD or number.

of CPB (samples 2 and 3, respectively). Urine samples were obtained at baseline (residual, sample A); after aortic cross-clamp release (sample B); and 2, 6, 24, 48, and 72 h after the termination of CPB (samples C, D, E, F, and G, respectively). Plasma and urinary samples were assayed for the proinflammatory cytokines IL-1β, TNFα, and IL-8, as well as the antiinflammatory cytokines IL-10, IL-1ra, and TNFsr2, using commercially available cytokine kits (Quantikine, R & D Systems Europe, Abingdon, Oxfordshire, United Kingdom). Urine was also assayed for NAG, creatinine, and α_1-microglobulin. NAG was analyzed by a spectrophotometric method using commercially available kits (PPR Diagnostics Ltd, London, United Kingdom) and α_1-microglobulin was analyzed by immunonephelometry (Beckman Coulter Ltd, High Wycombe, Buckinghamshire, United Kingdom).

Statistical Analysis

Data are presented as mean ± SD or median, percentiles, and range. The results were analyzed within groups compared with baseline using a nonparametric repeated measures analysis of variance with Dunn post-test as appropriate. *P* less than 0.05 was considered significant.

Results

All patients were similar with regard to demographic and perioperative data (table 1). Patients were known to have good left ventricular function with estimated left ventricular ejection fraction greater than 30%. Eleven patients received phenylephrine increments during CPB to maintain mean arterial pressure greater than 50 mmHg. Four patients required a dopamine infusion during the period immediately after bypass, which was continued in three patients until extubation (< 24 h) at a rate of 0–5 μg · kg^{-1} · h^{-1}. One patient required a norepinephrine infusion in the immediate postoperative period. Plasma creatinine concentrations for all patients were within the normal adult range (60–120 μM) preoperatively (94.9 ± 10.6 μM). Plasma creatinine concentrations decreased slightly at 24 h postoperatively (93.1 ± 17.5 μM) and then decreased to below preoperative levels at 48 h (85.7 ± 18.0 μM). Aprotinin was not administered to any patient.

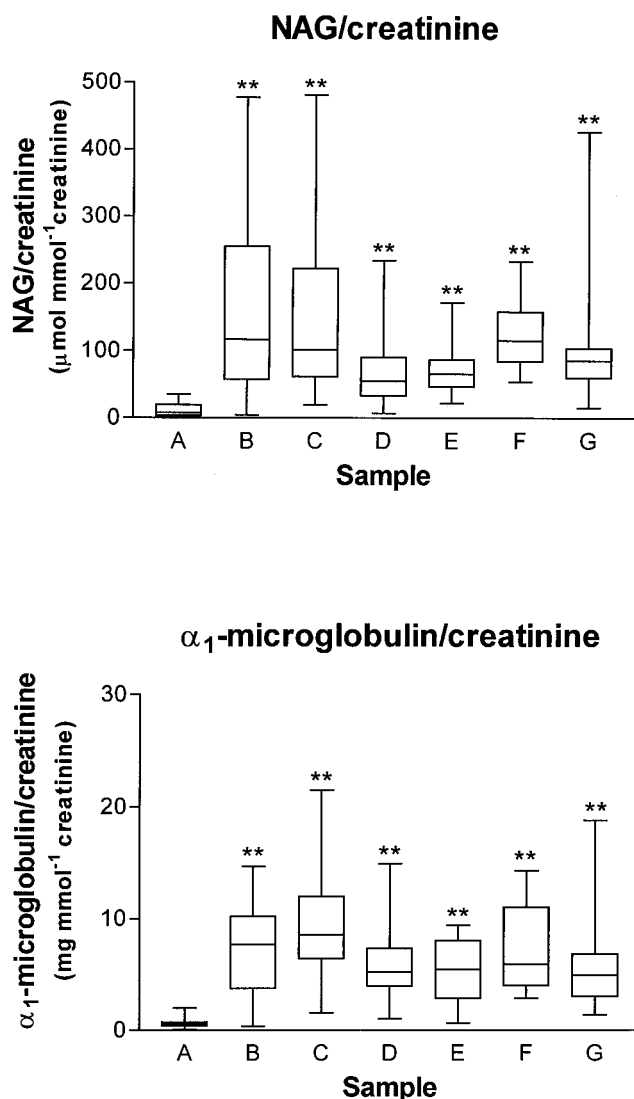## NAG/creatinine

α_1-microglobulin/creatinine

Fig. 1. Box and whisker plots of urinary *N*-acetyl-β-D-glucosaminidase (NAG)/creatinine and α_1-microglobulin/creatinine ratios. The top line of the box represents the 75th percentile, the bottom line represents the 25th percentile, and the middle line represents the 50th percentile or median. The whiskers represent the range. Sample A = baseline; sample B = after aortic cross-clamp release; sample C = 2 h after cardiopulmonary bypass (CPB); sample D = 6 h after CPB; sample E = 24 h after CPB; sample F = 48 h after CPB; sample G = 72 h after CPB. **P < 0.01 within group compared with baseline.

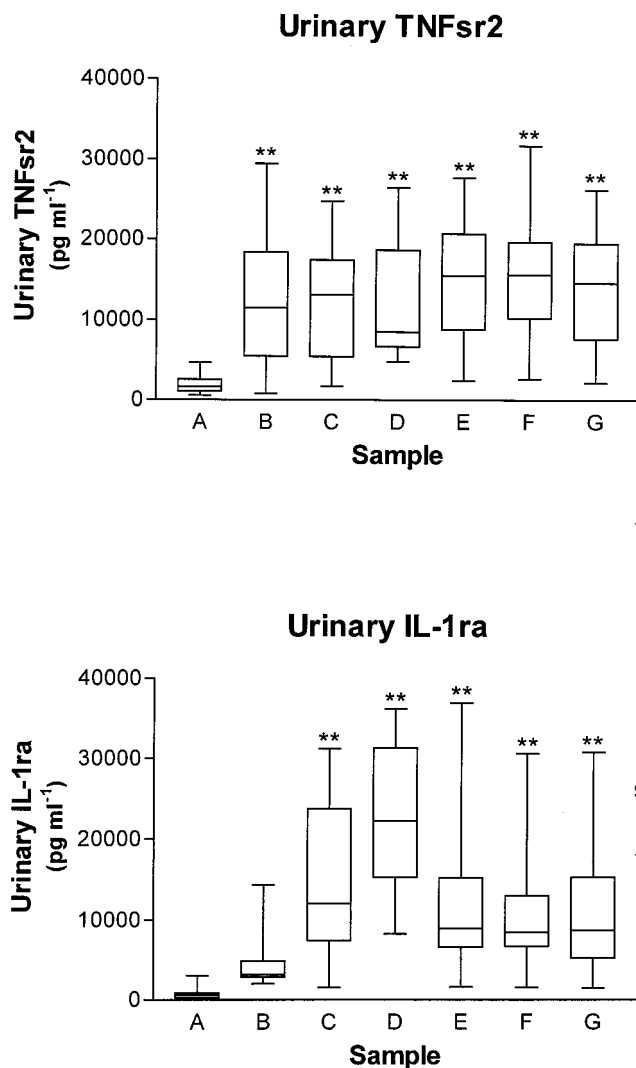## Urinary TNFsr2

Urinary IL-1ra

Fig. 2. Box and whisker plots of urinary tumor necrosis factor soluble receptor 2 (TNFsr2) and interleukin 1 receptor antagonist (IL-1ra) concentrations. The top line of the box represents the 75th percentile, the bottom line represents the 25th percentile, and the middle line represents the 50th percentile or median. The whiskers represent the range. Sample A = baseline; sample B = after aortic cross-clamp release; sample C = 2 h after cardiopulmonary bypass (CPB); sample D = 6 h after CPB; sample E = 24 h after CPB; sample F = 48 h after CPB; sample G = 72 h after CPB. **P < 0.01 within group compared with baseline.

Urinary Markers

Urinary NAG/creatinine ratios are shown in figure 1. There was an increase in NAG/creatinine ratio beginning after aortic cross-clamp release (sample B) and lasting for 2 h after CPB (sample C). Some recovery was noted at 6 and 24 h (samples D and E), but there was a further increase at 48 h (sample F), and levels remained elevated throughout the study period. All samples were significantly increased (P < 0.01) when compared with baseline.

Similar changes were also found in urinary α_1-microglobulin/creatinine ratios (fig. 1). There was a large increase beginning after aortic cross-clamp release (sample

B) that peaked at 2 h after CPB (sample C) with some recovery at 6 and 24 h (samples D and E), but a further increase occurred at 48 h (sample F), and levels remained elevated for the remainder of the study period. All samples were significantly increased (P < 0.01) when compared with baseline.

Urinary Cytokines

Urinary IL-1β, TNFα, IL-8, and Il-10 were detected in minimal amounts during the study period. Urinary TNFsr2 (fig. 2) was significantly elevated at all sampling times when compared with baseline (P < 0.01), whereas urinary IL-1ra (fig. 2) was also significantly increased at
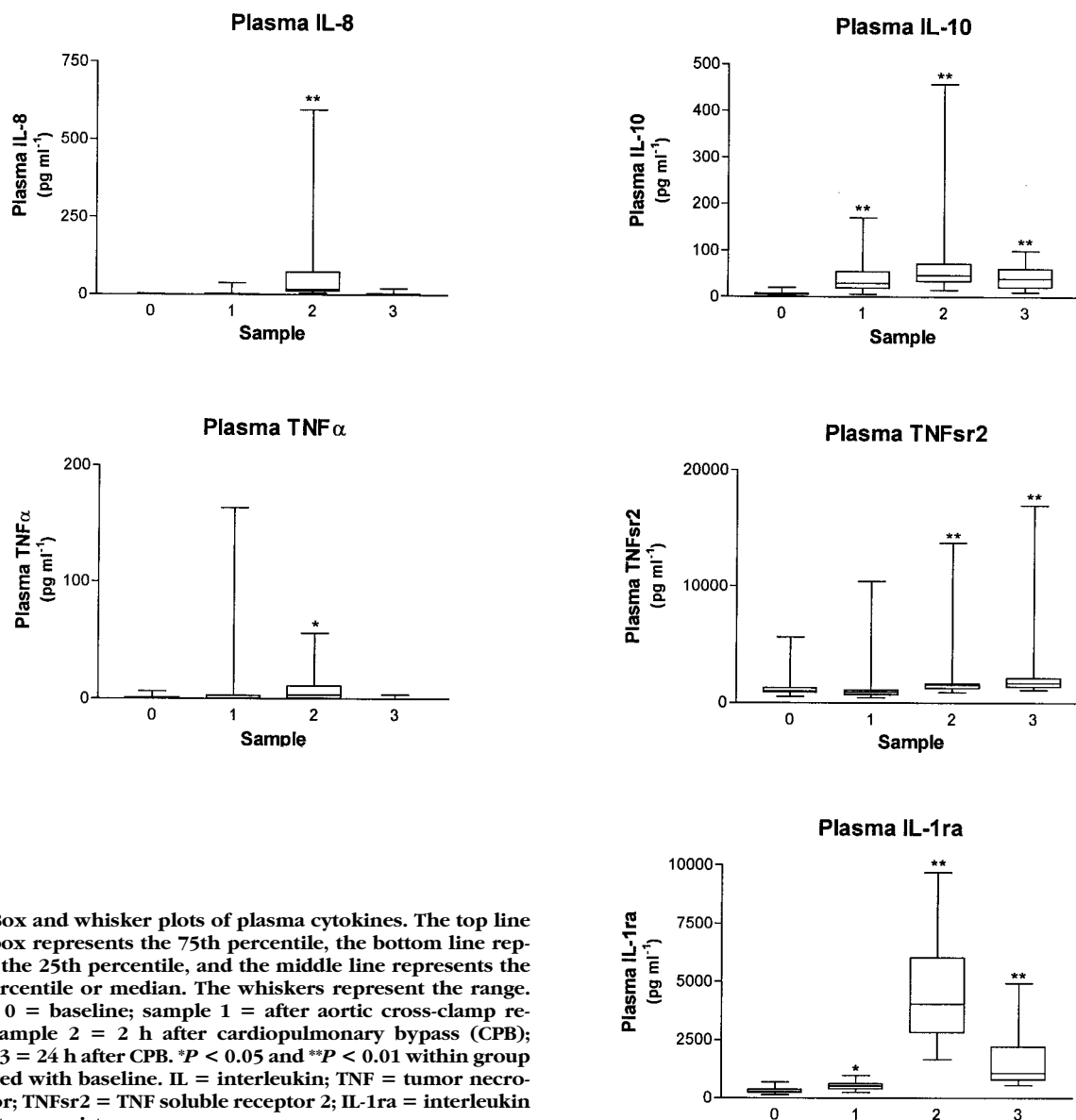
Fig. 3. Box and whisker plots of plasma cytokines. The top line of the box represents the 75th percentile, the bottom line represents the 25th percentile, and the middle line represents the 50th percentile or median. The whiskers represent the range. Sample 0 = baseline; sample 1 = after aortic cross-clamp release; sample 2 = 2 h after cardiopulmonary bypass (CPB); sample 3 = 24 h after CPB. *P < 0.05 and **P < 0.01 within group compared with baseline. IL = interleukin; TNF = tumor necrosis factor; TNFsr2 = TNF soluble receptor 2; IL-1ra = interleukin 1 receptor agonist.

all sampling times, apart from sample B (after aortic cross-clamp release), when compared with baseline (P < 0.01).

Plasma Cytokines

Plasma cytokine changes are illustrated in figure 3. TNF increased from baseline to a peak at cross-clamp release (sample 1) that was maintained at 2 h after CPB (sample 2) and returned to baseline values at 24 h after CPB (sample 3). IL-8 had a similar elevation with a maximum increase at 2 h after CPB (sample 2). IL-1β levels were below the lower detection limit of the assay throughout the study period. IL-1ra increased significantly from baseline in all samples, with a maximum increase at 2 h after CPB (sample 2). TNFsr2 also increased during the study, with a maximum increase compared with baseline at 24 h (sample 3). IL-10 dis-

played a similar pattern, being elevated in all samples when compared with baseline, with a peak increase at 2 h after CPB (sample 2).

Plasma TNFα concentrations at 2 h after CPB *versus* NAG/creatinine ratio at 2 and 6 h after CPB showed a significant correlation (Spearman rank correlation coefficient, 0.570 [P < 0.01] and 0.537 [P < 0.05], respectively). Plasma IL-8 concentrations at 2 h after CPB *versus* NAG/creatinine ratio at 6 h after CPB also showed a significant correlation (Spearman rank correlation coefficient, 0.494; P < 0.05). There was no correlation between α_1-microglobulin/creatinine ratios and plasma proinflammatory cytokines at any time point. Plasma TNFα concentrations at 2 h after CPB also correlated significantly with urinary IL-1ra concentrations at the same time point (Spearman rank correlation coefficient, 0.485; P < 0.05). Urinary IL-1ra concentrations and

NAG/creatinine ratios after cross-clamp release, 2 and 6 h after CPB, showed a significant correlation (Spearman rank correlation coefficient at cross-clamp release, 0.445 [$P < 0.05$]; at 2 h, 0.648 [$P < 0.01$]; at 6 h, 0.516 [$P < 0.05$]). There was no correlation between urinary TNFsr2 concentrations and NAG/creatinine ratios. There was also no correlation between urinary cytokines and α_1-microglobulin/creatinine ratios.

Discussion

The incidence of dialysis-dependent acute renal failure after cardiac surgery has been reported as 0.7–1.4%, with an overall mortality rate in these patients of 28–63.7%.[2,24,25] In addition, Conlon *et al.*[25] described a 7.9% incidence of non–dialysis-dependent renal dysfunction with a mortality rate of 1.8%. Although relatively uncommon, renal problems lead to a significant prolongation of postoperative recovery time with increased morbidity and mortality. Postoperative acute renal failure is more likely in patients older than 65 yr or after valve surgery or prolonged CPB time.[26] Recently, an appeal for urgent investigation into mechanisms of renal injury and dysfunction after cardiac surgery has been made.[24]

It has been shown recently that in patients undergoing cardiac surgery with normal preoperative renal function, as measured by plasma urea and creatinine, there is evidence of renal tubular dysfunction postoperatively. Westhuyzen *et al.*[6] described an elevation of urinary markers in almost all patients undergoing CPB, commencing during CPB and lasting for several days thereafter.[6] These included increases in concentrations of NAG, tubular brush border antigen, adenosine deaminase binding protein, and β_2 microglobulin. Jorres *et al.*[5] confirmed the aforementioned findings and also demonstrated an increase in α_1-microglobulin on day 1 after CPB, which remained elevated throughout the observation period of 5 days. It is therefore apparent that renal dysfunction after cardiac surgery forms a spectrum of severity ranging from the relatively uncommon development of dialysis-dependent acute renal failure to the almost universally occurring renal tubular dysfunction as measured by urinary markers such as NAG and α_1-microglobulin. In this study, we evaluated renal tubular dysfunction in a low-risk group of patients undergoing coronary artery revascularization grafting using NAG/creatinine and α_1-microglobulin/creatinine ratios. We found that patients had an increase in these urinary markers for several hours postoperatively but that there was some recovery at 24 h. There was a further peak in NAG/creatinine and α_1-microglobulin/creatinine ratios at 48 h that remained elevated when compared with baseline for the duration of the study period. Plasma creatinine concentrations remained within normal limits during the study period. This is consistent with previous published work by Westhuyzen

et al.[6] and Jorres *et al.*[5] confirming the presence of renal tubular dysfunction in the absence of overt changes in conventional measures of renal function.

Proinflammatory cytokines such as IL-1β and TNFα are usually detectable in plasma in low concentrations (< 10 pg/ml) or not at all. In contrast, the antiinflammatory cytokines, IL-1ra and TNFsr2, are normally detectable at plasma concentrations of greater than 600 pg/ml.[23,27] The maintenance of this constant plasma balance in favor of antiinflammatory cytokines has been called cytokine homeostasis.[18] Inflammatory cytokines may be found close to the site of production in local reservoir sites. If there is spillover of proinflammatory cytokines into the circulation, their proinflammatory effects are limited by plasma antiinflammatory cytokines that begin to increase in concentration.[23] The kidney preferentially filters the smaller proinflammatory cytokines (< 20 kd) and less readily filters the larger antiinflammatory cytokines (> 20 kd). During cardiac surgery involving CPB, there is an increase in plasma proinflammatory cytokines TNFα, IL-1β, and IL-8 as demonstrated in this and previous work.[23] These proinflammatory cytokines are then presented to the proximal renal tubules. Ordinarily, these small proinflammatory cytokines, although filtered at the glomerulus, are not excreted in the urine, and it has been demonstrated that they are absorbed by the proximal tubular cells and denatured by intracellular proteolytic mechanisms.[15,17] As the larger antiinflammatory cytokines (IL-1ra and TNFsr), which normally counterbalance the effects of these smaller proinflammatory cytokines, less readily pass into the glomerular filtrate, it was thought that during cardiac surgery involving CPB, the magnitude of the proinflammatory response would correlate with the magnitude of proximal tubular injury.

A general cytotoxic effect of proinflammatory cytokines has been suggested through iNOS induction.[28] Animal models of *in vitro* proximal tubular cultures have shown that challenge with lipolysaccharide or proinflammatory cytokines leads to induction of iNOS activity, suggesting a potential mechanism for proximal tubular damage during septicemia.[22,29,30] There are numerous studies identifying plasma TNFα as one of the proinflammatory cytokines associated with renal disease.[19,28] More specifically, the proinflammatory cytokines IL-1, TNFα, and interferon γ have been shown to induce iNOS in human proximal tubular cell culture, and the resultant nitric oxide is thought to be nephrotoxic.[21] These investigators suggested a time-dependent induction of iNOS as a mechanism of proinflammatory cytokine-induced proximal tubular damage in humans. Our study showed a positive correlation between the plasma TNFα concentrations 2 h postoperatively and the urinary NAG/creatinine ratios 2 and 6 h postoperatively. A correlation was also demonstrated between plasma IL-8 concentrations 2 h postoperatively and urinary NAG/creatinine ratios at

6 h postoperatively. The timings of these correlations would be in keeping with the results of Chatterjee *et al.*,[21] who suggested that proinflammatory cytokine-mediated proximal tubular damage is time and concentration dependent. This finding establishes a direct correlation between plasma TNFα and IL-8 concentrations and urinary NAG/creatinine ratios as a potential early indicator of renal dysfunction. Although NAG was elevated before plasma IL-8, this may have been in response to the early increase in TNFα, which correlated with the early NAG increase. Although IL-8 has not been investigated in proximal tubular cell culture for cytotoxicity, it is known to express its actions *via* iNOS induction.[31] Because the kidney is involved in removing proinflammatory cytokines from the circulation and denaturing them, a correlation between the plasma proinflammatory response and subsequent proximal tubular injury may not be unexpected.

Proinflammatory cytokines are more readily filtered than the larger antiinflammatory cytokines. We wished to determine if the kidney, in an attempt to maintain intrarenal cytokine balance, would, like the lung, rapidly generate a large endogenous protective antiinflammatory cytokine response, which would be detectable as an increase in urinary antiinflammatory cytokines.[27] This study demonstrated significant increases in the urinary antiinflammatory cytokines TNFsr2 and IL-1ra that preceded the increases in plasma antiinflammatory cytokines and occurred at a much greater magnitude. It is therefore apparent that the increases in urinary antiinflammatory cytokines cannot wholly be attributed to filtration of increased plasma antiinflammatory cytokines. We believe that the increased urinary antiinflammatory cytokines IL-1ra and TNFsr2 arise from sources within the renal tract. Because it is known that increases in plasma proinflammatory cytokines can stimulate the release of antiinflammatory cytokines from susceptible cells, we suggest that the arrival of proinflammatory cytokines in the glomerular filtrate early in the surgical process leads to activation of an intrarenal antiinflammatory cytokine response. This study demonstrated a positive correlation between plasma TNFα and urinary IL-1ra. It could be suggested that increased urinary antiinflammatory cytokines provide a mechanism in facilitating safe proximal tubular disposal of filtered plasma proinflammatory cytokines. The present study demonstrates that despite increases in plasma proinflammatory cytokines, there were no increases in urinary proinflammatory cytokines. This is consistent with the findings of Bocci,[15] that normally the kidney efficiently metabolizes filtered proinflammatory cytokines.

We also investigated if there was any relation between observed changes in urinary cytokines and renal tubular dysfunction. Simultaneous with the increase in urinary IL-1ra and TNFsr2, there was a significant increase in proximal tubular dysfunction as indicated by increased urinary NAG/creatinine and α_1-microglobulin/creatinine ratios. There was a positive correlation between the magnitude of the urinary IL-1ra and urinary NAG/creatinine ratio, suggesting a relation between the changes in urinary cytokine homeostasis and renal dysfunction. It is perhaps surprising that a urinary antiinflammatory cytokine, IL-1ra, should correlate with proximal tubular damage, because a direct causal relation is unlikely. However, it is likely that a common mechanism is contributing to both the antiinflammatory cytokines in the urine and the renal damage. A reason for this may be that the plasma proinflammatory cytokines, once filtered by the glomerulus, not only induce a degree of proximal tubular injury, but also at the same time trigger an intense intrarenal antiinflammatory response to allow the safe disposal of the proinflammatory cytokines.

This demonstration that changes in urinary cytokine balance accompany proximal tubular dysfunction will require further work to determine if a common mechanism is contributing to both changes, or if the changes in cytokine homeostasis result from, or contribute to, the renal tubular dysfunction. Although previous work has suggested that the kidney is involved in controlling the plasma proinflammatory response, the present study suggests that the kidney may itself be damaged by the very inflammatory response it is seeking to control. The results of this study also suggest that the kidney can rapidly mount an intense antiinflammatory cytokine response at the same time as it is filtering and destroying plasma proinflammatory cytokines.

References

1. Gailiunas P Jr, Chawla R, Lazarus JM, Cohn L, Sanders J, Merrill JP: Acute renal failure following cardiac operations. J Thorac Cardiovasc Surg 1980; 79:241–3

2. Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT: Renal dysfunction after myocardial revascularization: Risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. Ann Intern Med 1998; 128:194–203

3. Mazzarella V, Gallucci MT, Tozzo C, Elli M, Chiavarelli R, Marino B, Casciani C: Renal function in patients undergoing cardiopulmonary bypass operations. J Thorac Cardiovasc Surg 1992; 104:1625–7

4. Zanardo G, Michielon P, Paccagnella A, Rosi P, Calo M, Salandin V, Da Ros A, Michieletto F, Simini G: Acute renal failure in the patient undergoing cardiac operation: Prevalence, mortality rate, and main risk factors. J Thorac Cardiovasc Surg 1994; 107:1489–95

5. Jorres A, Kordonouri O, Schiessler A, Hess S, Farke S, Gahl GM, Muller C, Djurup R: Urinary excretion of thromboxane and markers for renal injury in patients undergoing cardiopulmonary bypass. Artif Organs 1994; 18:565–9

6. Westhuyzen J, McGiffin DC, McCarthy J, Fleming SJ: Tubular nephrotoxicity after cardiac surgery utilising cardiopulmonary bypass. Clin Chim Acta 1994; 228:123–32

7. Price RG: The role of NAG (N-acetyl-beta-D-glucosaminidase) in the diagnosis of kidney disease including the monitoring of nephrotoxicity. Clin Nephrol 1992; 38:S14–9

8. Price RG: Measurement of N-acetyl-beta-glucosaminidase and its isoenzymes in urine methods and clinical applications. Eur J Clin Chem Clin Biochem 1992; 30:693–705

9. Kunin CM, Chesney RW, Craig WA, England AC, DeAngelis C: Enzymuria as a marker of renal injury and disease: Studies of N-acetyl-beta-glucosaminidase in the general population and in patients with renal disease. Pediatrics 1978; 62:751–60

10. Dehne MG, Boldt J, Heise D, Sablotzki A, Hempelmann G: Tamm-Horsfall protein, alpha-1- and beta-2-microglobulin as kidney function markers in heart surgery. Anaesthesist 1995; 44:545–51

11. Flynn FV: Assessment of renal function: Selected developments. Clin Biochem 1990; 23:49–54

12. Davis CL, Kausz AT, Zager RA, Kharasch ED, Cochran RP: Acute renal failure after cardiopulmonary bypass is related to decreased serum ferritin levels. J Am Soc Nephrol 1999; 10:2396–402

13. Urzua J, Troncoso S, Bugedo G, Canessa R, Munoz H, Lema G, Valdivieso A, Irarrazaval M, Moran S, Meneses G: Renal function and cardiopulmonary bypass: Effect of perfusion pressure. J Cardiothorac Vasc Anesth 1992; 6:299–303

14. Gormley SMC, Young I, Armstrong MA, McMurray TJ, MacGowan SW, Campalani GF, McBride WT: Non-cardiopulmonary (CPB) cardiac surgery leads to significant proximal tubular dysfunction [abstract]. Br J Anaesth 1999; 83:176–7P

15. Bocci V: Interleukins: Clinical pharmacokinetics and practical implications. Clin Pharmacokinet 1991; 21:274–84

16. Bocci V, Paulesu L, Pessina GP: The renal catabolic pathways of cytokines. Contrib Nephrol 1993; 101:55–60

17. Poole S, Bird TA, Selkirk S, Gaines-Das RE, Choudry Y, Stephenson SL, Kenny AJ, Saklatvaa J: Fate of injected interleukin 1 in rats: Sequestration and degradation in the kidney. Cytokine 1990; 2:416–22

18. McBride WT, McBride SJ: The balance of pro- and anti-inflammatory cytokines in cardiac surgery. Curr Opin Anaesth 1998; 11:15–22

19. Kayama F, Yoshida T, Kodama Y, Matsui T, Matheson JM, Luster MI: Pro-inflammatory cytokines and interleukin 6 in the renal response to bacterial endotoxin. Cytokine 1997; 9:688–95

20. Meldrum DR, Donnahoo KK: Role of TNF in mediating renal insufficiency following cardiac surgery: Evidence of a postbypass cardiorenal syndrome. J Surg Res 1999; 85:185–99

21. Chatterjee PK, Hawksworth GM, McLay JS: Cytokine-stimulated nitric oxide production in the human renal proximal tubule and its modulation by natriuretic peptides: A novel immunomodulatory mechanism? Exp Nephrol 1999; 7:438–48

22. Markewitz BA, Michael JR, Kohan DE: Cytokine-induced expression of a nitric oxide synthase in rat renal tubule cells. J Clin Invest 1993; 91:2138–43

23. McBride WT, Armstrong MA, Crockard AD, McMurray TJ, Rea JM: Cytokine balance and immunosuppressive changes at cardiac surgery: Contrasting response between patients and isolated CPB circuits. Br J Anaesth 1995; 75:724–33

24. Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J: Independent association between acute renal failure and mortality following cardiac surgery. Am J Med 1998; 104:343–8

25. Conlon PJ, Stafford-Smith M, White WD, Newman MF, King S, Winn MP, Landolfo K: Acute renal failure following cardiac surgery. Nephrol Dial Transplant 1999; 14:1158–62

26. Mangos GJ, Brown MA, Chan WY, Horton D, Trew P, Whitworth JA: Acute renal failure following cardiac surgery: Incidence, outcomes and risk factors. Aust N Z J Med 1995; 25:284–9

27. McBride WT, Armstrong MA, Gilliland H, McMurray TJ: The balance of pro- and anti-inflammatory cytokines in plasma and bronchoalveolar lavage (BAL) at paediatric cardiac surgery. Cytokine 1996; 8:724–9

28. Yim CY, McGregor JR, Kwon OD, Bastian NR, Rees M, Mori M, Hibbs JB Jr, Samlowski WE: Nitric oxide synthesis contributes to IL-2-induced antitumor responses against intraperitoneal Meth A tumor. J Immunol 1995; 155:4382–96

29. Mayeux PR, Garner HR, Gibson JD, Beanum VC: Effect of lipopolysaccharide on nitric oxide synthase activity in rat proximal tubules. Biochem Pharmacol 1995; 49:115–8

30. Traylor LA, Proksch JW, Beanum VC, Mayeux PR: Nitric oxide generation by renal proximal tubules: Role of nitric oxide in the cytotoxicity of lipid A. J Pharmacol Exp Ther 1996; 279:91–6

31. Tavares-Murta BM, Cunha FQ, Ferreira SH: The intravenous administration of tumor necrosis factor alpha, interleukin 8 and macrophage-derived neutrophil chemotactic factor inhibits neutrophil migration by stimulating nitric oxide production. Br J Pharmacol 1998; 124:1369–74