Symposium: Clinical Research

Prognostic indicator by urinary microglobulin after renal stenting

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Objective To evaluate the effect of revascularization of the renal artery on urinary microglobulin in patients with coronary artery disease and significant renal artery stenosis (RAS). Methods Forty-four patients with coronary artery disease and severe RAS (luminal narrowing >70%) underwent percutaneous transluminal renal artery angioplasty (PTRA) and stenting, as well as percutaneous coronary intervention. The urine -microglobulin (α-MG) and β₂-microglobulin (β₂-MG) at baseline and at 3 months after the procedures were measured. Procedural success rate, procedural complications, serum creatinine concentration at baseline and at 3 months were also recorded. Results At 3 months after the renal revascularization therapy, there was no significant change of urine α-MG compared with that of the baseline, however, the urine β₂-MG decreased significantly 3-months after the treatment (237±187μg/L vs 377±173 μg/L, P<0.01). Multivariate analysis revealed that persistent elevation of urine was an independent predictor of severe events (including re-admission and renal failure) after renal revascularization therapy in patients with severe RAS (OR=3.01, 95% CI 1.01-8.95, P=0.036). Conclusions In patients with coronary artery disease and severe RAS, revascularization with PTRA and stenting may improve renal tubular function, but a continuous high level of urinary microglobulin after intervention is associated with more frequent re-hospitalization and renal failure.

Key Words: renal artery stenosis; percutaneous renal artery angioplasty; urinary microglobulin

Atherosclerotic renal artery stenosis (RAS) is frequently associated with ischemic nephropathy and renal dysfunction. The prevalence of renal artery stenosis as an underlying cause for end-stage renal disease is on the rise. When the mean blood pressure decreases to below a critical level (70 or 80 mmHg), autoregulation of renal blood flow becomes ineffective, and factors such as reduced shear stress and decreased production of nitric oxide, increased production of endothe1ins, and activation of the renin-angiotensin system may create localized areas of ischemia, tubular injury, epithelial-cell disruption, and interstitial fibrosis. In evaluation of the efficacy of percutaneous intervention in the treatment of RAS, most of the previous studies looked at end-points such as the serum creatinine concentration, glomerular filtration rate (GFR) or improvement of hypertension, few studies have addressed tubular function in RAS. In this perspective study, we compared the urine α₁-microglobulin (α₁-MG) and β₂-microglobulin (β₂-MG) before and after percutaneous renal revascularization in patients with coronary artery disease and RAS, to investigate the prognostic significance of tubular function in these patients.

Patients and Methods

Patient selection
From July 2002 through February 2003, 1,100 consecu-

Coronary and renal artery angiography and transluminal intervention
Patients received aspirin 100 mg/day and ticlodipine 500 mg/day before the procedure, at least for 3 consecutive days. Renal arteriography was performed following the coronary angiography. Protocols for coronary angiography, coronary
stenting, percutaneous renal artery angioplasty (PTRA) and stenting, and post-interventional management of patients in our center have been described previously.7

Measurement of urine $\alpha_1$-microglobulin and $\beta_2$-microglobulin

Urine sample was collected in the morning. Urinary $\alpha_1$-MG and $\beta_2$-MG concentrations were determined with competitive double antibody radioimmunoassay (JiuDing Company) on a Sn-682 radioimmunoassay γ reader. Concentrations of $\alpha_1$-MG <6μg/L and of $\beta_2$-MG <160 μg/L were defined as normal. In our laboratory, the mean concentrations of $\alpha_1$-MG and $\beta_2$-MG in 38 patients with coronary artery disease but without RAS were 3.2 ± 2.2μg/L and 159 ± 154μg/L, respectively.

Calculation of glomerular filtration rate

GFR was calculated according to the Cockcroft-Gault equation:

$$\text{GFR} \text{ (ml/min)} = \frac{(140 - \text{age in years}) \times \text{weight in kilogram}}{\text{serum creatinine (μmol/L)} \times 88.4 \times 72} \text{ (multiplied by 0.85 for women)}.$$

Study protocol and end points

The pre-interventional workup and all follow-up visits included measurement of serum creatinine, urinary $\alpha_1$-MG and $\beta_2$-MG, monitoring of blood pressure, documentation of major clinical adverse events (including renal failure and re-hospitalization), cardiac events (including cardiac death, myocardial infarction, and repeated revascularization of the target vessels), and the number and dosage of antihypertensive drugs. Follow-up examinations were scheduled before discharge and at 3 months after the intervention.

The primary end point was changes of the urine $\alpha_1$-MG and $\beta_2$-MG levels within 3 months of study entry. Other end points included blood pressure and serum creatinine concentration.

Statistical analysis

Discrete variables were expressed as counts, and comparison was done by $\chi^2$ test. Continuous variables were shown as mean±SD, comparisons within groups were performed by using Student t test. Logistic regression analysis was performed to assess factors associated with post-interventional severe adverse events (including re-hospitalization and renal failure).

Results

Patient characteristics at baseline and technical outcome

At baseline, compared with patients with mild RAS, those with severe RAS showed higher blood pressure (166±21mmHg vs 137±17mmHg, P<0.05), higher concentrations of urine $\alpha_1$-MG (5.2±2.5μg/L vs 3.0±2.7μg/L, P<0.01) and $\beta_2$-MG (377±173μg/L vs 202±184μg/L, P<0.001). They were more often found to have 3 vessel coronary lesions (23/44 vs 8/25, P<0.05). However, there was no significant difference between the two groups in terms of other clinical parameters (such as the prevalence of hypertension and diabetes, GFR and serum creatinine concentration) and types of coronary and renal stenosis.

In all of the 44 patients with 45 lesions, 46 stents were successfully implanted (with bilateral lesions in one patient and a long lesion in another). The procedural success rate was 100%. For the 79 coronary artery lesions in 40 patients (4 patients underwent coronary artery bypass graft), 66 stents were successfully deployed. In two patients, the guidewire failed to cross the total occlusive lesions, in another, the balloon could not pass the severely tortuous lesion.

Urine $\alpha_1$-MG and $\beta_2$-MG

In 40 patients who had been followed up for more than 3 months, the mean urinary $\beta_2$-MG concentration at 3 months after the procedure was 237±187μg/L, significantly lower than the baseline level (377±173μg/L, P<0.01). While the $\alpha_1$-MG concentrations did not change significantly (4.5±2.2μg/L at 3 months vs 5.2±2.5μg/L at baseline). In 22 patients with mild RAS, both $\alpha_1$-MG and $\beta_2$-MG concentrations had no significant changes.

Serum creatinine concentration and blood pressure

There was no significant change of serum creatinine concentration at 3 months after the intervention, compared with the baseline (99.3±18.3μmol/L vs 99.1±20.4μmol/L, P>0.05). However, blood pressure was improved in 25 of the 40 patients (defined as diastolic blood pressure <90mmHg and/or systolic blood pressure <140 mmHg on the same or reduced number of medications or reduced number of daily doses, or a reduction in diastolic blood pressure by at least 15 mmHg on the same or reduced number of medications). Twenty-one patients reduced their antihypertensive drugs and 4 patients were off the medications.

Procedural complications and outcomes of the patients

Serum creatinine concentrations elevated in 8 patients after the procedures (with the highest of 223μmol/L). In 7 patients, they returned to the pre-procedural levels at 2 weeks after the intervention, while in 1 patient it remained high 2 weeks after discharge. Thrombosis occurred in 1 patient after balloon dilatation of the renal artery lesion, but after the placement of the stent, appropriate blood flow was acquired. One patient experienced a lancing abdominal pain shortly after the procedure, which was alleviated by analgesics. Two patients died during the follow-up period, 1 from sudden death (presumably cardiac sudden death), 1 from severe infection after coronary bypass surgery. One patient had non-fatal myocardial infarction, and 2 received repeated coronary artery revascularization. No patient received repeated renal artery revascularization.

Predictors of severe adverse events

Logistic regression analysis was performed to identify the predicting factors of severe adverse events (including re-hospitalization and renal failure). Results showed that elevated urinary $\beta_2$-MG level which did not decrease from the pre-procedural level is an independent predictor for severe adverse events (OR=3.01, 95% CI 1.01~8.95, P=0.036).
Atherosclerosis is the major cause of RAS. In developed countries, it accounts for about 90 percent of cases of RAS. The prevalence of atherosclerotic RAS increases with age, particularly in patients with diabetes, aorto-iliac occlusive disease, coronary artery disease and hypertension.\(^1\)\(^8\)\(^8\)\(^8\) In patients referred for coronary angiography, for example, Khosla and colleagues\(^8\) found a prevalence of 19% of significant RAS (≥ 70% luminal diameter reduction) in those presented with refractory hypertension or flash pulmonary edema. In patients with angiographic coronary disease, about 15% showed hemodynamically severe RAS.\(^8\) In another population-based study of >800 free-living subjects who did not have recognized kidney disease and older than 65 years, renovascular disease of >60% lumen narrowing was present in 6.8%.\(^8\) Experimental studies demonstrate that even in mild renal stenosis, cortical and medullary perfusion is reduced.\(^8\) It was also shown that, compared with the glomerulus, the proximal tubule is more vulnerable to ischemia.\(^8\) Patients with RAS are often complicated by hypercholesterolemia, leading to impaired nitric oxide synthesis, activation of the renin-angiotensin system, increasing oxidative stress injury, and activating multiple inflammatory cytokines such as NF-kB. All these will further injure the tubular epithelium.\(^8\)

Most of the previous studies on renal stenosis focus on its effects on serum creatinine and GFR. However, serum creatinine may be at normal level in patients with unilateral RAS, even though ischemic injury has already occurred and the GFR reduced, as far as the opposite renal artery remained intact. In our study, serum creatinine was normal in patients with severe RAS, while the GFR only decreased slightly, a finding consistent with other reports.

Both α\(_1\)-MG and β\(_2\)-MG have been considered specific biomarkers of tubular injury. Urinary α\(_1\)-MG and β\(_2\)-MG increase in patients with tubular damage.\(^8\) In this study, the baseline urinary β\(_2\)-MG concentration in patients with severe RAS was significantly higher than that in mild RAS patients, indicating an association between renal stenosis and tubular dysfunction. After renal artery intervention, the urinary β\(_2\)-MG level was reduced, but α\(_1\)-MG level did not change, suggesting that in patients with RAS, endovascular intervention could only partly reverse tubular dysfunction.

Our study also found that re-hospitalization and renal failure were more frequent in patients with a continuous high level of urinary β\(_2\)-MG than in those whose urine β\(_2\)-MG decreased after the intervention. Further analysis with logistic regression showed that a continuous high level of urinary β\(_2\)-MG after renal artery intervention was an independent predictor of severe events in patients with atherosclerotic renal stenosis.

Atherosclerotic renal artery stenosis is often overlooked as a cause of renal insufficiency. Ischemic nephropathy is an important cause of end-stage renal disease, and among patients who are receiving dialysis, those with renovascular disease have a particularly poor prognosis. Serum creatinine concentration and GFR are poor indices of renal injury in renovascular patients. In our study, most of the patients showed normal serum creatinine concentrations and GFR, with no difference between patients with severe stenosis and those with mild stenosis. However, urine α\(_1\)-MG and β\(_2\)-MG levels were elevated in most of the patients with unilateral renal stenosis, indicating that urinary microglobulins may be more sensitive markers of the early renal ischemia. In a recent study, Perkovi and colleagues found that patients with elevated baseline serum creatinine levels have poor outcomes after renal artery stent implantation.\(^8\) Early intervention in RAS patients with normal GFR but elevated urinary microglobulins might be a strategy to improve patients’ survival and quality of life. However, further studies of larger samples and longer term are needed to evaluate the clinical significance of urinary microglobulins in patients with severe RAS.