Decrease of Glomerular Filtration Rate may be Attributed to the Microcirculation Damage in Renal Artery Stenosis

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Abstract

Background: The decrease of glomerular filtration rate has been theoretically supposed to be the result of low perfusion in renal artery stenosis (RAS). But the gap between artery stenosis and the glomerular filtration ability is still unclear.

Methods: Patients with selective renal artery angiogram were divided by the degree of renal artery narrowing, level of estimated glomerular filtration rate (eGFR), respectively. The different levels of eGFR, renal microcirculation markers, and RAS severity were compared with each other, to determine the relationships among them.

Results: A total of 215 consecutive patients were enrolled in the prospective cohort study. Concentrations of microcirculation markers had no significant difference between RAS group (RAS ≥ 50%) and no RAS group (RAS < 50%) or did not change correspondingly to RAS severity. The value of eGFR in RAS group was lower than that in the no RAS group, but it did not decline parallel to the progressive severity of RAS. The microcirculation markers presented integral difference if grouped by different eGFR level with negative tendency, especially that plasma cystatin C (cysC) and urinary microalbumin to creatinine ratio (mACR) increased with the deterioration of eGFR, with strong (r = −0.713, P < 0.001) and moderate (r = −0.580, P < 0.001) correlations. In the subgroup analysis of severe RAS (RAS ≥ 80%), the levels of plasma cysC and urinary mACR demonstrated stronger negative associations with eGFR, (r = −0.827, P < 0.001) and (r = −0.672, P < 0.001) correlations, respectively.

Conclusions: Severity of RAS could not accurately predict the value of eGFR, whereas microcirculation impairment may substantially contribute to the glomerular filtration loss in patients with RAS.

Key words: Glomerular Filtration Rate; Renal Artery Stenosis; Renal Microcirculation
Clinical characteristics of the patients with and without significant RAS

| Variables                              | RAS (RAS ≥ 50%) (n = 83) | No RAS (RAS < 50%) (n = 132) | Total (n = 215) | T   | P   |
|----------------------------------------|---------------------------|-----------------------------|-----------------|-----|-----|
| Age (years)                            | 69.51 ± 8.95              | 64.63 ± 11.21               | 66.55 ± 10.62   | 2.859 | 0.005 |
| Male, n (%)                            | 46 (55.4)                 | 93 (70.5)                   | 139 (64.7)      | 3.386 | 0.066 |
| Triple coronary vessel disease, n (%)  | 26 (31.3)                 | 60 (45.5)                   | 86 (40.0)       | 6.083 | 0.108 |
| Bilateral RAS, n (%)                   | 21 (25.3)                 | 21 (25.3)                   | 42 (24.0)       | -    | -   |
| Stenosis rate of renal artery (%)      | 77.28 ± 16.01             | 77.28 ± 16.01               | 77.28 ± 16.01   | -    | -   |
| eGFR (min⁻¹·1.73 m²)                   | 48.63 ± 24.94             | 59.36 ± 27.40               | 55.14 ± 26.90   | -2.466 | 0.015 |
| Chronic renal dysfunction (eGFR<60 ml·min⁻¹·1.73 m²), n (%) | 61 (73.5)                 | 74 (56.1)                   | 135 (62.8)      | 4.810 | 0.028 |
| Hypertension, n (%)                    | 80 (96.4)                 | 100 (75.8)                  | 180 (83.7)      | 12.278 | 0.000 |
| Diabetes mellitus, n (%)               | 34 (41.0)                 | 55 (41.7)                   | 89 (41.4)       | 0.004 | 0.95 |
| LVEF (%)                               | 61.79 ± 11.36             | 57.03 ± 12.68               | 58.90 ± 12.36   | 2.374 | 0.019 |
| NT-pro BNP (pg/mL)                     | 1629 ± 4187.43            | 2156.57 ± 4547.03           | 1949.22 ± 4402.75 | -0.727 | 0.469 |
| Serum β2-MG (mg/L)                     | 3.43 ± 2.67               | 3.05 ± 1.88                 | 3.20 ± 2.22     | 0.018 | 0.310 |
| Urinary β2-MG (mg/L)                   | 4.11 ± 10.09              | 3.21 ± 8.09                 | 3.56 ± 8.90     | 0.607 | 0.545 |
| CysC (mg/L)                            | 1.36 ± 0.85               | 1.31 ± 0.59                 | 1.33 ± 0.70     | 0.428 | 0.669 |
| UA (µmol/L)                            | 411.24 ± 124.57           | 394.43 ± 121.52             | 401.04 ± 122.60 | 0.834 | 0.406 |
| Urinary mACR (mgCr)                    | 157.16 ± 304.68           | 159.47 ± 441.33             | 158.56 ± 392.16 | -0.036 | 0.972 |

LVEF: Left ventricular ejection fraction; β2-MG: β2-microglobulin; CysC: Cystatin C; UA: Uric acid; Urinary mACR: Urinary microalbumin to creatinine ratio; RAS: Renal artery stenosis; eGFR: Estimated glomerular filtration rate; NT-pro BNP: N-terminal of the prohormone brain natriuretic peptide.
with severe lesion (RAS ≥ 80%), 10.2% (22/215) with moderate lesion (50% ≤ RAS < 80%), 24.2% (52/215) with mild lesion (50% > RAS > 0), and 37.2% (80/215) with normal artery (RAS = 0), respectively. The level of serum β2-MG in severe group was higher than those in the normal artery group (RAS = 0) (P = 0.011), with a weak positive associations to the severity of RAS (r = 0.172, P < 0.05), but it did not differ significantly in the three groups once lesions existed. Although they also lineated a positive relation trend, urinary mACR and other indexes of the microcirculation function did not make significantly variable no matter how the severity of RAS was Table 2.

Renal microcirculation function and estimated glomerular filtration rate level

Patients were grouped by eGFR into different renal functions status [Table 3]. More than half of the overall patients (62.8%, 135/215) had chronic renal dysfunction (eGFR < 60 ml·min⁻¹·1.73 m⁻²). The microcirculation markers mentioned above presented integral difference between normal function group (eGFR ≥ 90 ml·min⁻¹·1.73 m⁻²) versus severe dysfunction group (eGFR < 30 ml·min⁻¹·1.73 m⁻²). The values of microcirculation markers, however, were not significantly different between patients with normal (eGFR ≥ 90 ml·min⁻¹·1.73 m⁻²) and mild (90 > eGFR ≥ 60 ml·min⁻¹·1.73 m⁻²) impairment of renal function. The concentrations of urinary mACR and cystatin C increased with the deterioration of eGFR, with which they had moderate (r = −0.580, P < 0.001) and strong (r = −0.713, P < 0.001) correlations, respectively. In the subgroup analysis of patients with severe RAS (RAS ≥ 80%), all the microcirculation markers had significantly negative relation with eGFR level. Among them, levels of plasma cystatin C and urinary mACR demonstrated even stronger negative associations with eGFR, (r = −0.827, P < 0.001) and (r = −0.672, P < 0.001) correlations, respectively [Table 4].

### Table 2: Renal microcirculation markers in different RAS severity

| Variables                  | RAS ≥ 80% (n = 61) | 50% ≤ RAS < 80% (n = 115) | 0 < RAS < 50% (n = 99) | RAS = 0 (n = 90) | Statistical value | P     |
|----------------------------|--------------------|---------------------------|------------------------|-----------------|------------------|-------|
| Serum β2-MG (mg/L)         | 3.93 ± 3.20        | 2.59 ± 0.88              | 2.87 ± 1.60           | 3.09 ± 1.95     | 11.23            | 0.011 |
| Urinary β2-MG (mg/L)       | 5.10 ± 12.14       | 2.48 ± 4.74              | 5.42 ± 13.79          | 2.59 ± 5.65     | 4.68             | 0.196 |
| CysC (mg/L)                | 1.54 ± 1.02        | 1.07 ± 0.29              | 1.34 ± 0.58           | 1.30 ± 0.59     | 4.85             | 0.183 |
| UA (µmol/L)                | 419.57 ± 130.99    | 400.75 ± 116.25          | 374.87 ± 97.23        | 398.73 ± 126.77 | 1.136            | 0.768 |
| Urinary mACR (mg/mCr)      | 167.15 ± 322.17    | 146.93 ± 284.47          | 147.88 ± 245.78       | 160.47 ± 479.13 | 0.018            | 0.997 |

RAS: Renal artery stenosis; β2-MG: β2-microglobulin; CysC: Cystatin C; UA: Uric acid; Urinary mACR: Urinary microalbumin to creatinine ratio. Superscript letters *,† stand for a subset of the column group; different letter meant statistically different statistic values between groups, no statistical difference between with the same letter.

### Table 3: Renal microcirculation markers in different levels of eGFR in the total population

| Variables      | eGFR ≥ 90 ml·min⁻¹·1.73 m⁻² (n = 25) | 90 > eGFR ≥ 60 ml·min⁻¹·1.73 m⁻² (n = 54) | 60 > eGFR ≥ 30 ml·min⁻¹·1.73 m⁻² (n = 99) | eGFR < 30 ml·min⁻¹·1.73 m⁻² (n = 37) | Statistical value | P     |
|----------------|-----------------------------------|------------------------------------------|------------------------------------------|------------------------------------|------------------|-------|
| Serum β2-MG (mg/L) | 2.15 ± 0.53                      | 2.26 ± 0.73                              | 3.18 ± 1.29                              | 5.39 ± 4.17                       | 15.474           | 0.000 |
| Urinary β2-MG (mg/L) | 0.77 ± 0.58                      | 1.63 ± 4.03                              | 3.31 ± 8.10                              | 9.07 ± 15.28                      | 4.877            | 0.003 |
| CysC (mg/L)        | 0.84 ± 0.21                      | 0.95 ± 0.19                              | 1.33 ± 0.42                              | 2.23 ± 1.10                       | 34.936           | 0.000 |
| UA (µmol/L)        | 320.99 ± 107.59                  | 373.13 ± 127.52                          | 414.21 ± 109.41                         | 461.89 ± 125.79                   | 6.218            | 0.001 |
| Urinary mACR (mg/mCr) | 16.77 ± 20.28                   | 69.58 ± 179.15                           | 164.92 ± 350.53                         | 372.57 ± 689.02                   | 4.301            | 0.006 |

eGFR: Estimated glomerular filtration rate; β2-MG: β2-microglobulin; CysC: Cystatin C; UA: Uric acid; Urinary mACR: Urinary microalbumin to creatinine ratio. Superscript letters *,† stand for a subset of the column group; different letter meant statistically different statistic values between groups, no statistical difference between with the same letter.

### Table 4: Renal microcirculation markers in different levels of eGFR in severe RAS (RAS ≥ 80%)

| Variables     | eGFR ≥ 90 ml·min⁻¹·1.73 m⁻² (n = 5) | 90 > eGFR ≥ 60 ml·min⁻¹·1.73 m⁻² (n = 12) | 60 > eGFR ≥ 30 ml·min⁻¹·1.73 m⁻² (n = 28) | eGFR < 30 ml·min⁻¹·1.73 m⁻² (n = 16) | Statistical value | P     |
|---------------|-----------------------------------|------------------------------------------|------------------------------------------|------------------------------------|------------------|-------|
| Serum β2-MG (mg/L) | 1.82 ± 1.03                      | 2.16 ± 0.96                             | 4.32 ± 0.59                              | 7.39 ± 3.84                       | 18.519           | 0.000 |
| Urinary β2-MG (mg/L) | 1.91 ± 0.74                      | 2.98 ± 3.23                             | 6.64 ± 4.18                              | 15.43 ± 15.28                     | 9.649            | 0.000 |
| CysC (mg/L)    | 0.92 ± 0.13                      | 1.34 ± 0.18                             | 2.22 ± 0.57                              | 3.23 ± 0.76                       | 28.749           | 0.000 |
| UA (µmol/L)    | 356.47 ± 95.11                   | 388.63 ± 131.49                         | 436.26 ± 116.31                         | 543.84 ± 123.19                   | 7.361            | 0.000 |
| Urinary mACR (mg/mCr) | 32.57 ± 18.39                    | 102.71 ± 72.35                         | 384.13 ± 293.66                         | 548.96 ± 423.68                   | 11.873           | 0.000 |

β2-MG: β2-microglobulin; CysC: Cystatin C; UA: Uric acid; Urinary mACR: Urinary microalbumin to creatinine ratio; eGFR: Estimated glomerular filtration rate; RAS: Renal artery stenosis. Superscript letters *,†,‡ stand for a subset of the column group; different letter meant statistically different statistic values between groups, no statistical difference between with the same letter.
Severity of renal artery stenosis and renal function

The level of eGFR in RAS ≥ 80% group was significantly more impaired than that in the normal artery group (RAS = 0) (44.50 ± 27.88 vs. 60.09 ± 28.17 ml·min⁻¹·1.73 m², P = 0.011). And eGFR value did not have a significant difference in other groups comparisons, which indicated a weak negative associations between eGFR level and severity of RAS (r = −0.234, P < 0.001) [Figure 1].

DISCUSSION

Our study demonstrates that the stenotic extent of renal artery trunk, which was the golden diagnostic standard for RAS, was not that strongly related to the renal function impairment as theoretically conceived. The renal microcirculation markers presented as connection with RAS severity and renal function. Severity of microvascular damage and loss may determine the frontier before eGFR by promoting the progression of renal functional and structural damage.

The renal microcirculation has unique anatomical and functional characteristics. The renal artery small branching order afferent arterioles lead to the glomerular capillaries and the distal ends of the capillaries of each glomerulus join together to form the efferent arterioles, followed by a second capillary network constituted by the peritubular capillaries surrounding renal tubules.[7] The changes in tone in afferent and efferent arterioles and glomerular capillary pressure are the main determinants of GFR. The decrease in the availability of small vessels in the kidney can transiently or permanently deteriorate renal blood flow, glomerular filtration ability, and tubular function, which was suggested as a possible starting point of RAS.[8-10]

The reduction in renal perfusion attributable to RAS was acknowledged to be the essential cause of ischemic renal disease. Nevertheless, the results of revascularization of RAS were disconcerting that resolution of hypertension and mainly, improvements in renal function are still at best modest. The difficulty lies in that a high degree of stenosis may not correlate with deteriorative renal function or deserve refractory hypertension.[11,12] And reasons for this gap between the success rate and outcomes are mainly in the microvascular disease and parenchyma damage distal to the stenosis. In addition to diagnosis confirmed, it could be more important to interpret the “significant” and “reversible” RAS, including the complex relation between anatomy and function.

Although one could hypothesize that RAS would be associated with lower perfusion and more severe renal function impairment, we found only a weak negative association between eGFR level and severity of RAS in the study. Since GFR is determined by both renal blood flow and glomerular capillary hydrostatic pressure, the severity of RAS displayed only weak association with eGFR. The rising systemic blood pressure triggered by renin-angiotensin-aldosterone system could compensate the hemodynamic effects of stenotic lesions, regulation of afferent, and efferent arteriole could temporary maintain the glomerular filtration ability, not every RAS would then lead in renal ischemia and influence the eGFR result. Resolution of the stenosis did not always recover renal function, which had been observed in human and experimental studies.[13,14] For the overall population in the present study, all microcirculation markers presented variable degree of difference between normal function group versus severe dysfunction group, whereas not significant difference was observed between normal renal function group and mild renal dysfunction group. It indicated that in the early impairment of eGFR, the renal parenchyma loss was still limited, and RAS or the microvascular disease deserves aggressive treatment. The deterioration of eGFR may be reversed by the reconstruction of perfusion. However, in patients with moderately to severely impaired eGFR, microcirculation biomarkers would negatively correlate with eGFR. Furthermore, in the subgroup analysis of patients with severe RAS (RAS ≥ 80%), microcirculation biomarkers presented even more prominent negative association with all eGFR level, indicating the potential causal relationship between reduced glomerular filtration ability and microcirculation dysfunction in patients with RAS, especially for those with severe RAS. With the more severe stenotic lesion in renal artery, there would be more diffuse disease in the microvascular and more loss of the renal parenchyma.

Renal microvasculature remodeling and damage could directly compromise the perfusion of glomerulus and mesenchymal, leading to the glomerular sclerosis and interstitial fibrosis.[15,16] Functional abnormalities in the microcirculation of the renal parenchyma distal to the stenosis in RAS contribute to the pathophysiology of ischemic renal real injury.[17,18] Although assessment of the severity of RAS could be technically resolved with the use of the clinically available high-resolution imaging techniques (e.g., computed tomography angiography, selective angiography), the assessment and quantification of renal microcirculation

![Figure 1](image_url): Comparison of estimated glomerular filtration rate in patients divided by increasing severity of renal artery stenosis.
damage are, on the other hand, the most difficult problem to sort out. Stromski et al. had found out missing pulse steady state free precession as a powerful tool for the noninvasive measurement of slow flows in different regions of the kidney about renal microcirculation, while some laboratory indexes recently are adopted as the detection of microvasculature damage in renal microcirculation dysfunction, like 24 h microalbuminuria (mALB), transferrin, β2-MG, urinary retinal binding protein, urinary N-acetyl-β-D-glucosamine, cysC, UA, and urinary mACR. Notably, all the microcirculation markers in our study had prominent elevation by increasing severity of eGFR. CysC is a new and promising biomarker for kidney microcirculation dysfunction. Because of its low molecular weight, cysC is freely filtered at the glomerulus and is almost completely reabsorbed and catabolized, but not secreted by tubular cells. The elevation of cysC concentration, not influenced by inflammation, age or sex, reflected the early decrease of glomerular filtration rate. Given these characteristics, cysC concentration may be superior to creatinine concentration in detecting renal function impairment. In the present study, the cysC could not differentiate the RAS group from no RAS group, but it showed a strong relation with eGFR. Meanwhile, the term mALB was coined to describe a small increase in the level of albumin of normal urine protein, which represented the early impairment of endothelial function and renal microcirculation. Previous data had revealed that spot urinary mACR accurately reflects the total 24 h level of urine albumin excretion and the mACR has been shown to be superior to a 24 h urine collection in predicting renal events in patients with type 2 diabetes and nephropathy. Likewise, mACR level was not significantly different in the RAS and no RAS group, the level of mACR, however, also had apparent relation to eGFR. Both of cysC and mACR indicated that microvascular disease was not absolutely parallel to the main trunk lesion, and the mere application of stenotic rate of renal artery could not accurately represent the real deterioration status. Microcirculation presented as the conjunction between the eGFR and RAS severity, adding more comprehensive information to the RAS.

Deterioration of the renal microcirculation in the chronically stenotic kidney could play a pivotal role in defining the “significant” RAS. The presence of functional microcirculation impairment may indeed represent the initial steps of renal injury. Beyond the stenotic degree of artery, serum cysC and urinary mACR emerged as compromising biomarkers in RAS systemic evaluation and could complement information for clinical management.

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