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Baseline inflammatory status and long-term changes in renal function after percutaneous renal artery stenting: A prospective study

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ABSTRACT

Objectives: To investigate a possible independent predictive role of systemic inflammation markers on renal function after renal artery stenting.
Background: An elevated baseline serum creatinine has previously been shown to be the strongest predictor of improved renal function after percutaneous renal artery stenting. The inflammatory system is implicated in every stage of chronic kidney disease, and we hypothesized an additional value of markers of systemic inflammation in predicting response after renal artery stenting.
Methods: This single center, prospective study includes 62 consecutive patients with chronic kidney disease at stage ≥3 or resistant hypertension who underwent stent placement for 74 angiographically significant atherosclerotic renal lesions. Inflammatory markers, including serum C-reactive protein (CRP), erythrocyte sedimentation rate, and white blood cell count were determined prior to renal angioplasty and related to changes in renal function at follow-up.
Results: Six-month clinical follow up was completed in 57 patients. Overall, median serum creatinine concentration exhibited a non significant reduction from 1.40 mg/dl (quartiles: 1.20, 1.75 mg/dl) at baseline to 1.30 mg/dl (quartiles: 1.1, 1.55 mg/dl) at 6 months ($p=0.17$). Significant multivariate independent predictors of decreased creatinine included higher baseline serum creatinine levels (adjusted OR per quartile increment, 2.5 [1.3 to 4.7], $p=0.004$) and lower C-reactive protein levels (adjusted OR per quartile increment 0.39 [0.19 to 0.82], $p=0.013$).
Conclusions: Patients with higher serum creatinine and lower CRP derive the most benefit from renal artery stenting.

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1. Introduction

Renal artery stenosis (RAS) is a common manifestation of peripheral vascular disease, contributing to the poorly controllable hypertension and the high incidence of chronic kidney disease (CKD) frequently observed in advanced atherosclerosis patients [1]. Percutaneous stenting is rapidly gaining acceptance as treatment of choice for atherosclerotic RAS, yet its effects on renal function are variable, with at least one fourth of the treated patients experiencing worsening of renal function at follow-up [2]. Moreover, there is little data on the key question of identifying predictors of improved renal function at long-term follow-up [3,4]. As systemic inflammation is implicated in both atheroma development [5] and worsening of CKD over time [6], and is also associated with complications and mortality in end-stage CKD [7], we hypothesized that evaluation of inflammation may also help in identifying "responders" to renal artery stenting.

Thus, the aim of this prospective study was to evaluate the effect of percutaneous revascularization on renal function in a cohort of patients undergoing stent placement for CKD ≥stage 3 with severe RAS and to assess whether markers of systemic inflammation could help predicting the benefit of renal artery stenting.

2. Methods

2.1. Patient population

This single center, prospective study includes consecutive patients undergoing stent placement for atherosclerotic renal ostial stenosis. During a 5-year period (June 2002 to June 2007), we enrolled at our Institution 62 patients undergoing stenting of atherosclerotic stenosis of at least one renal artery. Assessment of renal artery stenosis was based primarily on duplex ultrasound scan, subsequently confirmed by quantitative angiography showing a percent diameter stenosis >70% in all cases.

Main inclusion criteria were CKD stage ≥3 according to the NKF DOQUI classification [8] and/or severe hypertension (defined as hypertension not controlled despite

Abbreviations: RAS, renal artery stenosis; CKD, chronic kidney disease; CRP, serum C-reactive protein; ESR, erythrocyte sedimentation rate; CIN, contrast-induced nephropathy; GFR, glomerular filtration rate; EF, eject fraction; ACE, angiotensin converting enzyme.

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administration of ≥3 antihypertensive drugs). CKD staging was based on estimated glomerular filtration rate (eGFR) according to the simplified MDRD method [9]. Patients who had been on a hemodialysis program and those who did not provide informed consent to participate were excluded. Our institutional ethics committee approved the study.

Clinical and angiographic data were recorded for each patient. Our sample was drawn from a population with high prevalence of severe significant multisite arterial vascular disease, defined as the presence of at least one significant stenosis (≥70% in diameter) in coronary, carotid or lower limb vascular territory assessed by either angiography or ultrasound scan. Left ventricular function was assessed by left ventricular angiography or echocardiography if angiography was not available. Global left ventricular ejection fraction was determined by the area–length method and coded as reduced left ventricular function if <45%.

All patients undergoing stenting received double antiplatelet therapy with acetylsalicylic acid (160 mg daily) plus clopidogrel (75 mg daily) or ticlopidine (500 mg daily) started 48 h before and continued for at least 1 month after the procedure, oral N-acetylcysteine (1200 mg), and intravenous hydration with sodium bicarbonate 1 h before the procedure and for the next 6 h according to standard protocol [10]. Significant multisite arterial involvement in coronary, carotid or lower limb vascular territory was detected in 79% of patients (coronary 69%, lower limb 40%, carotid 18%) and 44 patients (71%) underwent non-renal artery angioplasty, mainly in a separate session.

2.2. Renal artery stent placement

Seventy-four renal artery stenosis (12 bilateral, 19%) were treated in 62 patients (27 female, 44%). All procedures were performed under continuous electrocardiographic and invasive blood pressure monitoring. Forty-five arteries were approached by transradial vascular access (62%, right 45% and left 55%), and 29 (38%) by transfemoral access. Primary success of the procedure was defined as residual percent diameter stenosis <30% by quantitative computerized angiography and was achieved in 73/74 procedures: a short total occlusion could not be crossed with the guidewire in a patient with bilateral stenosis, whereas the contralateral RAS was successfully treated.

2.3. Study protocol

The preinterventional workup included among routine checks was measurement of serum creatinine and inflammatory markers. C-reactive protein was measured using a high-sensitivity latex-enhanced immunonephelometric assay (Latex/BN II, Dade Behring, Marburg, Germany). The working range of the assay was 0.175 to 1100 mg/l, and the coefficient of variation was <5%. The median normal value for CRP is 0.8 mg/l, with 90% of normal values <3 mg/l. Erythrocyte sedimentation rate (ESR, in mm/h) was measured using Westergren tubes. Complete red and white blood cell counts were also obtained from the Hospital's hematology department. Serum creatinine was measured again at 48 h after the renal intervention. Clinical follow-up was routinely obtained at 6 months after the index intervention, and serum creatinine measurement was repeated at the same hospital.

2.4. Study endpoints and definitions

The primary end-point of our study was the incidence of any decrease in serum creatinine concentration at 6 months, considered as dichotomous (yes/no) variable. This conservative definition of improved renal function was chosen due to its validation in previous studies, as opposed to definitions based on eGFR [4]

Secondary endpoints were the absolute change in creatinine and eGFR between baseline and 6 months, or Δcreatinine and ΔGFR, and the development of contrast-induced nephropathy (CIN), defined as an absolute increase in creatinine levels of more than 25% at 48 h compared to the baseline value (CIN 25), as this definition was consistently associated with adverse events at follow-up in a comparison analysis [11].

2.5. Statistical analysis

Discrete variables were expressed as counts, and comparison was done by chi-square test. Unless stated otherwise, we show continuous variables as mean ± SD. The Kolmogorov–Smirnov test showed that creatinine concentrations, changes in creatinine concentration, and CRP values were not normally distributed. Hence, creatinine concentration is shown as median (interquartile range) and differences between baseline and 6 months were tested by using 2-way ANOVA on log-transformed data. To identify univariate and multivariate predictors of the primary and secondary end points, we performed logistic regression analysis. The model included age and sex (background variables), reduced left ventricular function, statin treatment, ACE-inhibitor use, number of sites with concomitant atherosclerosis, diameter stenosis, presence of diabetes mellitus, CRP concentrations (in quartiles), bilateral stenting, and baseline serum creatinine (in quartiles) according either to literature showing plausible links with CKD progression or renal artery stenting efficacy [1,2,4], or findings at univariate analysis (variables with $p<0.1$ were entered into the model).

Stepwise forward logistic regression with likelihood-ratio test was used. The goodness-of-fit testing (Hosmer and Lemeshow χ^2) assessed how well the final model was calibrated. SPSS statistical package (SPSS Inc, Chicago, IL), version 15.0, was used. All hypothesis testing was 2 tailed. Probability values of $p<0.05$ were considered significant.

3. Results

Baseline characteristics and measured variables for the entire cohort and stratified for the primary endpoint are reported in Table 1.

3.1. Improvement of renal function: univariate analysis

The primary end point, reduction in serum creatinine concentration during 6-month follow-up, was reached in 30 of 57 patients (52%). Median serum creatinine concentration exhibited a non significant reduction from 1.40 mg/dl (quartiles: 1.20, 1.75 mg/dl) at baseline to 1.30 mg/dl (quartiles: 1.1, 1.55 mg/dl) at 6 months ($p=0.17$). Univariate logistic regression identified higher baseline serum creatinine and lower CRP (Fig. 1 and Table 1) as the only variables significantly associated with reduced creatinine at follow-up.

In general, the decrease in serum creatinine concentration tended to be larger the higher the baseline serum creatinine. When baseline creatinine was stratified according to median values, patients with a serum creatinine concentration at study entry >1.4 mg/dl ($n=29$) had a median decrease in serum creatinine concentration by 0.30 mg/dl (quartiles: −0.5, 0.05 mg/dl), whereas those with serum creatinine concentration at study entry <1.4 mg/dl ($n=28$) had no change in serum creatinine concentration (median = 0.01 mg/dl, quartiles: −0.1, 0.35 mg/dl). This difference between the 2 strata was largely significant (2-way ANOVA time-baseline creatinine interaction; $p<0.0001$) (Figs. 2 and 3).

Contrary to baseline creatinine, the decrease in serum creatinine concentration at follow-up tended to be larger the lower the baseline CRP (Figs. 4 and 5). When baseline CRP was stratified according to median values, patients with a CRP concentration at study entry <3.1 mg/dl ($n=28$) had a median decrease in serum creatinine concentration by 0.20 mg/dl (quartiles: −0.5, 0.07 mg/dl), whereas those with CRP concentration at study entry >3.1 mg/dl ($n=29$) had no significant change in serum creatinine concentration (median = 0 mg/dl, quartiles: −0.1, 0.2 mg/dl). This difference between the 2 strata was significant (2-way ANOVA time-CRP interaction; $p=0.038$).

3.2. Improvement of renal function: multivariate analysis

Significant multivariate independent predictors of improved renal function were higher on baseline serum creatinine levels (adjusted OR per quartile increment, 2.5 [1.3 to 4.7], $p=0.004$) and lower on C-reactive protein levels (adjusted OR per quartile increment 0.39 [0.19 to 0.82], $p=0.013$). The Hosmer–Lemshow goodness of fit test showed a non significant value ($p=0.55$), indicating that the model was adequate, and the pseudo-R^2 value of the final model was 0.446, indicating a good predictive value. In particular, CRP was selected as the second predictor after baseline creatinine, with a significant variation in the pseudo-R^2 value (from0.284 to 0.446, $p=0.032$), indicating that CRP conferred an additional 17% predictive value to the logistic regression model.

Considering Δcreatinine as a continuous variable, we fitted a linear regression model using log-transfomed CRP and log-transformed baseline creatinine to further check for an independent predictive value of the two variables. The entire model was significant and predicted about 40% of the entire delta creatinine variability ($R^2=0.39$, $p<0.001$). Despite being moderately correlated among themselves (Pearson's $r=-0.27$, $p=0.028$), the two variables showed a significant and independent predictive value for delta creatinine (beta = −0.4, $p=0.001$ for baseline creatinine and beta = 0.4, $p=0.001$ for baseline CRP).

Regarding ΔGFR, another linear regression model was fitted using log-transformed CRP and baseline GFR as independent variables. As expected, the entire model was significant and predicted 50% of the entire ΔGFR variability ($R^2=0.49$, $p<0.001$). The two variables were only moderately correlated among themselves (Pearson's $r=0.35$, $p=0.03$), and showed a significant and independent predictive value

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