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Predictor factors for renal outcome in renal artery stenosis

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Abstract. – BACKGROUND: Atherosclerotic ischemic renal disease is a frequent cause of end-stage renal failure. Correction of renal artery stenosis (RAS) may fail to stabilize or improve renal function.

AIMS OF THE STUDY: Carotid and aortic Intima media thickness (IMT), resistance renal resistance index (RI), arterial blood pressure (BP), serum creatinine (SCr), creatinine clearance (Cr-Cl), proteinuria and uricemia were considered as possible predictive factors and measured before renal-artery stenosis correction and during 12 months follow-up.

MATERIALS AND METHODS: we performed an observational study on a total of 55 patients to find predictive factors of the outcome of renal function after renal percutaneous transluminal angioplasty and stenting (RPTAs).

RESULTS: We found that uricemia, proteinuria and IR were higher at baseline in patients who worsened renal function after revascularization.

CONCLUSIONS: The identification of predictive factors (uricemia; proteinuria and RI) of chronic kidney disease (CKD) progression in patients with RAS undergone revascularization could be useful to predict renal long term outcome and to select patients that really could benefit of this.

Key Words:
Renal artery angioplasty and stenting, Renal artery stenosis, Intima media thickness, Resistance index.

Introduction

Renal artery stenosis (RAS) is a recognized cause of hypertension and renal failure[1].

In most cases revascularization improves arterial blood pressure but fails to improve and/or stabilize renal function[2]. Despite the arterial dilatation obtained with these procedures is mostly successful[3], patients with atherosclerotic renovascular disease have a high rate of systemic atherosclerosis and are at increased risk for adverse cardiovascular outcomes[4].

The identification of predictive factors of progression of chronic kidney disease (CKD) in patients with RAS undergone revascularization could be useful to predict renal long term outcome and to select patients that really could benefit of this procedure.

Radermacher et al[5] showed that the resistance index (RI) predicts renal outcome in patients with RAS undergone revascularization. Pignoli et al[6,7] showed that intima media thickness (IMT) was a sonographic marker for early atherosclerotic vascular wall lesions related to generalized atherosclerosis[8-10]. In end-stage renal failure it was correlated with cardiovascular risk[11].

Recent studies suggested that uricemia and proteinuria are important predictors of renal outcome. Hyperuricemia induces arteriolopathy of preglomerular vessels which impairs the autoregulatory, lumen obliteration producing severe renal hypoperfusion[12] with tubulointerstitial inflammation, fibrosis and arterial hypertension.

Proteinuria is a common finding in patients with ischemic nephropathy with urinary protein excretion rates of less than 1 g/die to severe 24 h proteinuria[13] and is the major determinant of renal dysfunction in patients with renal ischemia[14,15]. In patients with renal ischemia and coexisting proteinuria, the prognosis worsens with the increase of proteinuria[16]. The risks of mortality, myocardial infarction and progression to kidney failure are increased in patients with higher proteinuria levels[17].

Since poor is known about the predictive effect of these echographic (RI and IMT) and metabolic risk factors of kidney disease in patients with

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renal percutaneous transluminal angioplasty and stenting (RPTAs), we conducted an observational study on this issue.

Materials and Methods

Patients and Study Design

We performed an observational study on a total of 55 patients that referred to our Nephrology Unit between 2007 and December 2009 for significant (at least 70%) atherosclerotic, mono or bilateral, RAS to undergo RPTAs.

Exclusion criteria were: non significant stenosis (< 70%), non atherosclerotic or dysplastic stenosis and restenosis. Diabetic patients were not selected for this study to exclude other causes of proteinuria. Patients with atrial fibrillation, aortic valve insufficiency, nephritis, and other diseases, who did not allow a reliable measurement of the RI, were excluded from the study.

All patients were undergone to RPTAs.

Before and after RPTA and monthly for 1 year, all patients were undergone laboratory tests, carotid, aortic and renal arteries ecocolor Doppler.

Renal Percutaneous Transluminal Angioplasty and Stenting

For RPTAs the renal artery was approached through a skin incision in the femoral artery. We used 5-French catheters for selective renal-artery angiography and 7-8 French guiding catheters for positioning the stent. All lesions were repaired with stainless steel Palmaz-Schatz stents (AVE, Bard Saxx Palmaz 6-15/20, Miami Lakes, FL, USA) pre-mounted on a balloon catheter.

For RPTAs, patients received an injection containing 35-40 mL of a 50-50 mixture of isotonic contrast and normal saline.

Laboratory Tests

Patients underwent routine laboratory tests: creatinine, blood urea nitrogen, sodium, potassium, calcium, fosforum, uric acid, cholesterol, triglyceride plasma levels, proteinuria/24 hours.

Glomerular filtrate rate (GFR) was calculated with the 4-variable MDRD[18] .

GFR (mL/min/1.73 m^2) = 175 × SCr -1.154 × Age -0.203 × 0.742 (if woman) × 1.21 (if black).

Carotid and Aortic Artery Intima Media Thickness

Common carotid (CC IMT) and aortic artery intima media thickness (AA IMT) were measured from the images obtained by an ultrasound machine (Toshiba Aplio® Ultrasound System, Tokyo, Japan; SSA-790) equipped with a high-resolution 3.5 Mhz vascular transducer and 7.5-linear-array transducer as originally described by Pignoli et al[7]. All scans were performed by the same sonographer (R.C.). The longitudinal 2D images were obtained at the proximal 1- to 2 cm from bifurcation of the right and left common carotid artery, and 4 and 8 cm from aorto-iliac bifurcation. IMT was defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface[8]. These measurements were made at end diastole. At least 6 measurements of IMT were taken at each segment (carotid and aortic) and the mean values were used for analysis. Plaque was defined as a localised irregular thickening at least of 1.5 mm[9].

Renal Resistance Index

We measured the resistive index (RI) for both kidneys ([1 - end-diastolic velocity ÷ maximal systolic velocity] × 100); and in two subsets by color Doppler ultrasonography (CDU). We calculated the mean resistance index value for the two kidneys[5].

Endpoint

End point was a decrease of eGFR more than 20% from basal after 1 year follow-up.

Definitions

Hyperuricemia was defined as defined as serum uric acid levels greater than greater than 7.7 mg/dl in man and greater than 6.6 mg/dl in woman[19].

CKD was defined as eGFR < 60 ml/min/1.73[20] m^2.

Proteinuria was defined as proteinuria > 300 mg/die[21].

Statistical Analysis

Statistical analysis was performed by the SPSS program for Windows, version 18.0 (SPSS Inc, Chicago, IL, USA).

Continuous variables are presented as mean ± standard deviation (SD), and categorical variables are presented as absolute numbers and/or percentages. Data were checked for normality before statistical analysis with the Wilks and Shapiro test. Categorical variables were analysed using either the chi-square test or Fischer's exact test. Comparison between and within groups was made using analysis of variance (ANOVA) and Bonferroni's correction. *p* values were considered significant if < 0.05.

Results

Of 55 patients that referred to our Nephrology Unit between 2007-2009 for RAS only 53 patients were eligible for the study because two patients died during the follow-up.

Basal demographic and clinical characteristics are reported in Table I.

All patients received medical therapy including: statins and anti-hypertensive drugs (antiangiotensin agents, calcium channel blockers and beta-blockers). All patients were treated with 2 ± 1 anti-hypertensive drugs. After procedure antiplatelet agents (acetylsalicylic or ticlopidine + clopidogrel) were also prescribed.

One patient died for procedure-related haemorrhage.

After procedure CDU showed that in 51of 55 patients (92.7%) stents were patent. One patient (1.8%) had a residual stenosis after revascularization that was treated by aorto-renal by-pass six months later. One patient (1.8%) presented early restenosis that was not treated.

One (1.8%) patient presented acute renal failure soon after the procedure and needed dialysis for three months.

One patient died (1.8%) after six months for cancer.

Table I. Basal demographic and clinical caratheristics of patients.

Age, years (mean ± SD*)	65.5 ± 7.8
Men, n (%)	33 (62.26)
Systolic BP, mmHg (mean ± SD*)	169.6 ± 22.9
Diastolic BP, mmHg (mean ± SD*)	89.3 ± 15.4
Creatinine, mg/dl (mean ± SD*)	2.01 ± 0.9
Cr. Clearance, ml/min (mean ± SD*)	41.5 ± 25.3
Azotemia, mg/dl (mean ± SD*)	68.6 ± 37.3
Sodium, mEq/L (mean ± SD*)	140.3 ± 4.3
Potassium, mEq/L (mean ± SD*)	4.2 ± 0.5
Proteinuria, mg/24h (mean ± SD*)	327.6 ± 332.4
Severity of stenosis (%)	> 70%
Bilateral stenosis, n (%)	8 (15)
Controlateral occlusion, n (%)	5 (9.4)
Smoker, n (%)	28 (52.83)
Hypertension, n (%)	52 (98.11)
Hyperuricemia, n (%)	22 (41.5)
Perpherial artheriopathy, n (%)	34 (64.15)
Dyslipidemia, n (%)	30 (56.6)
Cholesterol mg/dl (mean ± SD*)	235.8 ± 32.4
Trygliceridi mg/dl (mean ± SD*)	179.8 ± 91
Max- IMT CCA (mean ± SD*)mm	1.1 ± 0.1
RI (mean ± SD*)	0.74 ± 0.03

Legend: BP: Blood pressure; Cr: creatinine; RI: Resistance Index; AA IMT: abdominal aortic intima media thickness; CC IMT: common carotid intima media thickness. *SD: standard deviation.

After 1 year 53 patients are reached the end of follow-up. Analysis of the data showed that: 17 patients (32%) presented a decrease of CrCl >20% from basal value (Group A: worsened renal function), 18 patients (34%) an increase of eGFR > 20% from basal value (Group B: improved renal function) and 18 patients (34%) had a eGFR equal to basal value (Group C: stabilized renal function).

Among the three groups there were not significant differences in age, basal systolic and diastolic blood pressure, prevalence of periferic arteriopathy, dyslipidemia, bilateral and controlateral occlusion.

The prevalence of smokers was significantly higher in worsened than improved and stabilized patients ($p < 0.005$).

Worsened Patients

In worsened patients, after 1 year follow-up median serum creatinine concentration significantly dropped from 1.9 ± 0.5 mg/dL at baseline to 2.68 ± 0.9 mg/dL ($p < 0.001$) and CrCl significantly decreased from 37.5 ± 12 ml/min to 24.7 ± 9.7 ml/min ($p < 0.001$).

Proteinuria and and serum uric acid levels were significantly higher in worsened patients than improved and stabilized patients ($p < 0.05$).

Proteinuria significantly increased after 1 years from 494.3 ± 342.5 mg/24h at baseline to 2609.4 ± 2047.4 mg/24h after 1 year follow-up ($p < 0.001$). Three patients (2.5%) had proteinuria in nephrotic range at the end of follow-up.

CC IMT and AA IMT was higher in worsened and stabilized than improved patients ($p < 0.05$). RI was higher in worsened than improved and stabilized patients ($p < 0.05$).

Improved Patients

In improved patients median serum creatinine concentration decreases significantly from 2.46 ± 1.2 mg/dL at baseline to 1.7 ± 0.7 mg/dL at 1 year ($p < 0.001$) and CrCl significantly increased from 33.2 ml/min ± 20.6 to 51.8 ± 22.5 ml/min ($p < 0.001$). No significant change in proteinuria was found after 1 year (baselinee 157.6 ± 122.7 mg/24h vs 1 year follow-up 111.1 ± 102.5 mg/24h) ($p = 0.7$).

Stabilized Patients

In stabilized patients median serum creatinine concentration and CrCl unchanged (creatinine: baseline 1.56 ± 0.6 mg/dL vs 1 year follow-up

1.6 ± 0.8 mg/dL; $p = 0.236$) (CrCl: baseline 53.9 ± 33.6 ml/min vs 1 year follow-up 53.7 ± 32.7 ml/min; $p = 0.817$).

Proteinuria worsened after 1 year but not significantly (256.3 ± 339.7 mg/24h at baseline to 500.6 ± 406.6 mg/24h after 12 months follow-up; $p = 0.07$).

In all three groups, serum uric acid levels, IMT and RI uric acid serum level, IMT and RI did not change significantly after 1 year follow-up, while the mean systolic and diastolic blood pressure significantly decreased.

Statistical Correlation

A significant positive correlation was found between uricemia and proteinuria ($p = 0.02$). Uricemia was correlated with RI only in stabilized ($p = 0.04$) and in worsened patients ($p = 0.02$) but not in improved patients ($p = 0.6$).

It is not significantly correlated with CC IMT ($p = 0.1$) but significantly correlated with AA IMT ($p = 0.005$).

There was a significant positive correlation between proteinuria and RI ($p = 0.006$). Proteinuria is not significantly correlated with AA IMT ($p = 0.06$).

We found that CC IMT was significantly correlated with AA IMT ($p < 0.0001$) and RI ($p < 0.0001$).

CC IMT was not significantly correlated both with proteinuria ($p = 0.05$) and with uricemia ($p = 0.1$). Tables II and III summarize the results of statistic correlations.

Discussion

Renal artery stenosis is a leading cause of secondary hypertension and renal failure. In the last 10 years revascularization improved outcome of patients with RAS but the effects of this procedure are not still clear on long term renal function.

Dorros et al[22] in 1998 and Lederman et al[23] in 2001 showed an improve of renal function in high percentage of patients with atherosclerotic RAS after RTPAs.

Furthers anatomical factors, biochemical and genetics factors play a role in the progression of renal failure after RPTAs[24].

Perkovi et al[25] identified as risk factors for an unfavorable outcome diabetes mellitus, advanced age and renal failure, while the use of ACE inhibitors following the stenting procedure was protective toward death or deterioration of renal failure.

In this study we analyzed the predictive effects of some biochemical factors and echographic index.

In our patients age, basal systolic and diastolic blood pressure, peripheric artheriopaty, dyslipidemia, bilateral and contralateral occlusion were not associated with poor renal outcome after revascularization. Also CrCl and creatinine were not predictive index of renal outcome after RPTAs.

A significant statistical correlation was found among CC IMT, basal serum uric acid and and the others study index (proteinuria, RI and AA IMT). A better outcome were associated with lower levels of uricemia, RI, CCA and AA IMT, while a worsened outcome was related with elevated RI and uricemia, that confirm to be also markers of renal atherosclerosis.

Uric acid is an end product of purine metabolism that is generated during enzymatic degradation of hypoxanthine and xanthine to uric acid[26]. The kidney is dominant in the elimination of uric acid and hyperuricemia is usually caused by inadequate renal excretion of uric acid[27]. Many epidemiological and animal studies have found that hyperuricemia confers a high susceptibility to CKD[28]. Sanchez-Lozada LG et al[12] showed that mild hyperuricemia induced in rats arteriopathy with impaired capacity of preglomerular vessels to maintain glomerular pressure since arterial hypertension. In addition, lumen obliteration induced by vascular wall thickening results in severe vasoconstriction, decreasing renal plasma flow, GFR, and perfusion to peritubular capillaries.

Table II. Statistical correlations among CC IMT and the studied index.

CC IMT before RPATs	RI	Proteinuria	Uricemia	IMT AA
	p value	*p* value	*p* value	*p* value
Total of the patients	< 0.0001	0.05	Ns	< 0.0001
Stabilized	< 0.0006	0.005	0.02	< 0.001
Improved	< 0.0002	Ns	Ns	< 0.001
Worsened	Ns	Ns	Ns	< 0.001

Legend: RI: Resistance Index; AA IMT: abdominal aortic intima media thickness; CC IMT: common carotid intima media thickness.

Table III. Statistical correlations among uricemia and the others studied index. The bold characters shown statistically correlation among variables studied.

Uricemia before RPATs	RI	Proteinuria	CC IMT	AA IMT
	p value	*p* value	*p* value	*p* value
Total of the patients	0.09	0.02	Ns	0.005
Stabilized	0.04	0.006	0.02	0.01
Improved	Ns	Ns	Ns	Ns
Worsened	0.02	Ns	Ns	Ns

Legend: RI: Resistance Index; AA IMT: abdominal aortic intima media thickness; CC IMT: common carotid intima media thickness.

The resulting ischemia is a potent stimulus that induces tubulointerstitial inflammation and fibrosis, as well as arterial hypertension.

As well as also proteinuria is an important risk factor of progression and some Authors suggested a possible causal relationship between chronic ischemia and the development of secondary focal segmental glomerular sclerosis, with consequent severe proteinuria in patients with RAS[29]. Glomerular lesions resembling focal glomerulosclerosis have been reported in patients with RAS[30]. The increase in proteinuria following stenting should probably be attributed to increased perfusion pressure in damaged sclerotic glomeruli[1]. According with this we note a worsened proteinuria in patient with an elevated RI (at east of 0.80).

RI has been associated, in several studies, with cardiovascular and renal disease[31]. A predictive value has been assigned to this index, but is not clear the relationship between renal RI, blood pressure and renal function response after revascularization for atherosclerotic renovascular disease. Some Authors[32] describe as RI is associated with renal function but not blood pressure response while a strong, independent relationship between RI and mortality was observed.

CC and AA IMT correlated with RI both in improved that in stabilized patients. This correlation was not more present in worsened patients. We suggest that RI in these patients is modified from local factors that does not modify CC IMT.

These data confirm that IMT is a systemic index of atherosclerotic process, associated with other cardiovascular index and risk factors[33-36], but it doesn't seem to be related to kidney renovascular disease.

At last a significant drop in systolic and diastolic blood pressure at all control times compared to basal values was found in all the patients of the tree groups except for the improved group where a normal value of diastolic was present since before RPTAs.

Conclusions

We suggest that before revascularization should be observed and treated with appropriate therapy the factors that have been shown to have predictive value on renal outcome as hyperuricemia and proteinuria.

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