Original Article

Frequency and Predictors of Renal Artery Stenosis in Patients Undergoing Simultaneous Coronary and Renal Catheterization

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Received 29 November 2011; Accepted 27 February 2012

Abstract

Background: Atherosclerotic renal artery stenosis (ARAS) remains underdiagnosed due to its nonspecific demonstrations. We aimed to both estimate the frequency of ARAS in high-risk non-selected patients undergoing simultaneous coronary and renal catheterization and possibly identify a predictive model for ARAS using baseline clinical, laboratory, and coronary angiographic variables.

Methods: The records of 866 patients aged ≥ 21 years undergoing simultaneous coronary and renal angiography were retrieved for analysis from our computerized database. The degree of ARAS was estimated visually by experienced attending interventional cardiologists. Lesions with an estimated stenosis of $\geq 50\%$ were considered significant. Multivariable stepwise logistic regression models were used to identify the risk factors predicting the presence and extent of ARAS.

Results: Of a total of 866 consecutive patients undergoing renal angiography in conjunction with coronary angiography (mean age \pm SD: 63.06 \pm 10.32, ranging from 24 to 89 years), 454 (57%) were men. A total of 345 (39.8%) cases had significant ARAS, 77 (22.3%) of which were bilateral. Using significant ARAS as the dependent variable, six variables were identified as the independent predictors significantly associated with the presence of ARAS, namely age, female sex (male sex was found to be a protector), hypertension, history of renal failure, left anterior descending artery (LAD) stenosis > 50%, and left circumflex artery (LCX) stenosis > 50%. The Gensini score was not found to be a predictor of the presence of ARAS, but it was more likely associated with a trend towards a more extensive ARAS (adjusted OR = 1.00, 95% CI = 1.00-1.01; p value = 0.039). Other independent determinants of the ARAS extent were the same as the predictors of the ARAS presence.

Conclusion: Although risk versus benefit was not tested in this study, it seems that clinicians could consider renal catheterization in combination with coronary angiography particularly in female patients with advanced age and with significant coronary artery stenoses in the LAD and LCX.

J Teh Univ Heart Ctr 2012;7(2):58-64

This paper should be cited as: Rokni N, Salarifar M, Hakki Kazazi E, Goodarzynejad HR. Frequency and Predictors of Renal Artery Stenosis in Patients Undergoing Simultaneous Coronary and Renal Catheterization. J Teh Univ Heart Ctr 2012;7(2):58-64.

Keywords: Renal artery obstruction • Coronary angiography • Renal insufficiency

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Introduction

Renal artery stenosis is a potential cause of secondary hypertension, ischemic nephropathy, and end-stage renal disease. Atherosclerosis is by far the most common etiology of renal artery stenosis in the elderly.^{1, 2} Although as the narrowing of the renal artery lumen progresses, renal perfusion declines and eventually renal function and structure are compromised,^{3, 4} patients with atherosclerotic renal artery stenosis (ARAS) are often asymptomatic with no characteristic laboratory findings, making its early diagnosis a major clinical problem. Paradoxically, diagnosis of ARAS at an early stage is of paramount importance because despite the uncertainty that exists about the benefit of revascularization over medical therapy for ARAS,⁵ it has been demonstrated that timely intervention using revascularization technique, surgery, or percutaneous transluminal angioplasty (PTA) may modify the natural history and outcomes.⁶

ARAS and coronary artery disease (CAD) originate from similar multiple risk factors for the development of atherosclerosis so that not surprisingly patients with ARAS more commonly have CAD and vice versa.7-10 Presence of ARAS worsens the course of CAD, leading to increased risk of adverse coronary events, more frequent episodes of coronary revascularization, and higher mortality.¹¹⁻¹³ Because of the high coexistence of CAD and ARAS in patients with angiographically documented CAD,^{9, 10} it has been recommended that renal angiography be performed consecutively in the same setting.¹⁴ However, operators are reluctant to perform renal angiography in combination with coronary angiography for several reasons: renal angiography is an invasive method; it can result in the dislodgment of the atheromatous debris; and it has severe complications, including contrast-associated nephropathy.

Therefore, identifying patients at high risk for ARAS in patients referred for coronary angiography is of great clinical importance and may influence treatment decisions in this population. We sought to find the independent determinants of the presence of significant stenosis in one or both renal arteries with a view to estimating the frequency of ARAS in high-risk non-selected patients undergoing simultaneous coronary and renal catheterization and possibly identifying a predictive model for ARAS using baseline clinical, laboratory, and coronary angiographic variables.

Methods

Between October 2009 and July 2011, a total of 18419 cardiac catheterizations were performed at our center. Clinical and procedural data were prospectively collected and entered into a computerized database on all patients undergoing cardiac catheterization at Tehran Heart Center. The records of 866 (4.7%) patients aged ≥ 21 years

undergoing simultaneous coronary and renal angiography, representing our study population, were retrieved for analysis. The indication for renal angiography was at the discretion of the attending interventionist, but the procedure was mostly performed in patients with severe or resistant hypertension and renal dysfunction or in those suffering from pulmonary edema with preserved systolic function. Due to the retrospective nature of the study, requirement for written informed consent was waived by the institutional Ethics Committee.

Definition of CAD risk factors has been described previously.¹⁵ In brief; analyzed risk factors of CAD included age, male sex, cigarette smoking, hyperlipidemia, diabetes, hypertension, and family history of CAD. Patients having angiographic evidence of atherosclerosis (\geq 50% luminal stenosis in at least one coronary artery or major branch segment in their epicardial coronary tree) were considered to have CAD, and patients with no luminal stenosis or patients with < 50% luminal stenosis at coronary angiography were considered to have normal coronary.

Renal function was evaluated by serum Cr and CrCl, calculated using the Cockcraft-Gault equation. In all the patients, serum Cr level in mg/dl was determined before the procedure. The following equation was used: CrCl = $(140 - age [y]) \times weight (kg) \times 0.85$ (if female) / (serum Cr [mg/ dL] \times 72)

The calculated value of CrCl was multiplied by the factor of 0.85 in the female patients because the proportion of muscle mass to body weight is relatively lower in women than in men. The Cockroft-Gault equation was adjusted for the body surface area (BSA) by multiplying it by (1.73/ BSA) and expressed compared to the average sized man as mL/min/1.73 m². The BSA itself was calculated using the following DuBois formula: BSA (m²) = (weight [kg])^{0.425} × (height [cm])^{0.725} × 0.007184.¹⁶

Using standard angiographic techniques, coronary angiographies were performed via the percutaneous femoral approach. The presence and severity of CAD was determined using the clinical vessel score. The angiograms were categorized as revealing < 50% luminal stenosis (minimal CAD) or as having one (mild), two (moderate), or three (severe) major epicardial coronary arteries with more than 50% luminal obstructions. The left main stem (LMS) stenosis was regarded as one vessel. If the LMS and the left anterior descending (LAD) and/or left circumflex (LCX) arteries were affected, this was counted as 2 points. The visually determined greatest reduction percentage of the luminal diameter in any view compared with the nearest normal segment was defined as the degree of stenosis.

After the completion of their cardiac catheterization procedure, the patients underwent either selective or non-selective renal angiography. Abdominal aortography was performed using a pigtail catheter and an injection of 30 to 35 ml of nonionic contrast agent (Ultravist-370, Shering AG,

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Germany; or Visipaque-320, GE Healthcare, Ireland) with a pump injector at a rate of 20 ml/sec. Selective angiography was encouraged in patients with renal dysfunction, hypertension, and severe CAD, and generally 5 or 6 Fr catheters - renal double curve (RDC), right Judkins coronary, or left internal mammary artery (LIMA) catheters - with hand injections of 7 to 10 ml of nonionic contrast agent (Ultravist-370, Shering AG, Germany; or Visipaque-320, GE Healthcare, Ireland) were employed in each main and accessory renal artery. The degree of ARAS was estimated visually by experienced attending interventional cardiologists. Lesions with an estimated stenosis of \geq 50% were considered significant.

The results are reported as mean \pm standard deviation (SD) for the quantitative variables, and the categorical variables are summarized by absolute frequencies and percentages. The continuous variables were compared using the one-way analysis of variance (ANOVA) or Kruskal-Wallis test, whenever the data were ordinally scaled or when equal variances assumption was violated, while the categorical variables were compared using the chi-square test or Mantel-Haenszel chi-square test for trend.

factors predicting the presence of ARAS were expressed as odds ratios (OR) with 95% CIs as well. Using multivariable stepwise analysis, the variables were entered into the logistic regression model based on their statistical significance in the univariable analyses (entering criterion: p value ≤ 0.15). Amongst the Cumulative Logit Models for Ordinal Responses, the Proportional Odds Model was applied for the factors associated with the extension of ARAS (the ordinal response), which is the most commonly used model as the multivariable analysis.¹⁷ In the final model, the associations between the independent predictors and the extension of ARAS were also expressed as odds ratios (OR) with 95% CIs.

For the statistical analyses, the statistical software SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL) and SAS version 9.1 for Windows (SAS Institute Inc., Cary, NC, USA) were utilized. All the p values were two-tailed, with statistical significance defined by a p value ≤ 0.05 .

Results

Of a total of 866 consecutive patients undergoing renal

Table 1 Baseline clinical characteristics of the study population*

Multivariable stepwise logistic regression models for risk

	No RAS** (n=521)	Unilateral RAS (n=268)	Bilateral RAS (n=77)	P value
Age (y)	61.60±10.31	64.51±10.01	67.92±9.36	< 0.001
Male sex	311 (59.7)	146 (54.5)	37 (48.1)	0.093
Body mass index (kg/m ²)	28.14±4.94	28.14±4.92	26.37±4.49	0.017
Waist circumference (cm)	102.18±11.38	102.26±10.48	97.42±10.99	0.009
Hypertension	393 (75.4)	228 (85.1)	66 (85.7)	0.002
Diabetes	189 (36.3)	111(41.4)	28 (36.4)	0.355
Hyperlipidemia	359 (68.9)	218 (68.8)	58 (75.3)	0.477
Current smoker	120 (23.0)	46 (17.2)	12 (15.6)	0.082
Family history of CAD	88 (16.9)	40 (14.9)	6 (7.8)	0.114
History of MI	177 (34.0)	102 (38.1)	30 (39.0)	0.431
History of renal failure	63 (12.1)	52 (19.4)	22 (28.6)	< 0.001
History of hemodialysis	6 (1.2)	3 (1.1)	4 (5.2)	0.042
History of PVD	29 (5.6)	19 (1.1)	9 (11.7)	0.119
History of CVA	3 (5.8)	10 (3.7)	11 (14.3)	0.002
History of heart failure	24 (4.6)	13 (4.9)	2 (2.6)	0.691
Drug history				
ACE-inhibitors	213 (40.9)	123 (45.9)	36 (46.8)	0.315
Beta-blockers	398 (76.4)	204 (76.1)	56 (72.7)	0.780
Statins	319 (61.2)	173 (64.6)	43 (55.8)	0.352
Insulin	38 (7.3)	37 (13.8)	10 (13.0)	0.009
Prior PCI	32 (6.1)	18 (6.7)	3 (3.9)	0.661
Prior CABG	25 (4.8)	14 (5.2)	5 (6.5)	0.812

*Data are presented as mean \pm SD or n (%)

**Renal artery stenosis < 50%

RAS, Renal artery stenosis; CAD, Coronary artery disease; MI, Myocardial infarction; PVD, Peripheral vascular disease; CVA, Cerebrovascular accident; ACE, Angiotensin-converting enzyme; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass graft

Table .2 Laboratory and coronary angiographic characteristics of the studied pat	ients*
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	No RAS** (n=521)	Unilateral RAS (n= 268)	Bilateral RAS (n=77)	P value
Fasting blood glucose (mg/dl)	121.52±51.55	130.26±60.79	121.14±30.39	0.132
Triglyceride (mg/dl)	159.47±92.83	173.99±151.20	160.94±82.31	0.764
HDL-cholesterol (mg/dl)	42.14±11.48	42.98±12.81	41.11±11.47	0.649
DL-cholesterol (mg/dl)	110.55±37.96	109.80±40.11	121.19±41.07	0.153
otal cholesterol (mg/dl)	177.92±45.16	179.99±50.95	188.92±47.22	0.212
reatinine (mg/dl)	1.27±0.81	1.49±1.29	1.66±1.49	0.001
crCl-c (mL/min/1.73m ²)	69.19±27.70	60.90±29.78	49.27±21.13	< 0.001
AD vessel score				< 0.001
< 50%	142 (27.3)	33 (12.3)	6 (7.8)	
Single-vessel disease	103 (12.8)	37 (13.8)	13 (16.9)	
Two-vessel disease	94 (18.0)	56 (20.9)	15 (19.5)	
Three-vessel disease	182 (34.9)	142 (53.0)	43 (55.8)	
eft main	18 (3.5)	14 (5.2)	6 (7.8)	0.161
AD	329 (63.1)	213 (79.5)	64 (83.1)	< 0.001
CX	246 (47.2)	188 (80.1)	53 (68.8)	< 0.001
CA	262 (50.3)	174 (64.9)	55 (71.4)	< 0.001
ensini score	52.37±52.29	72.24±58.35	83.79±66.33	< 0.001
VEF (%)	50.05±11.63	49.46±11.34	48.40±11.74	0.312
IbA1c (%)	8.09±1.75	7.91±1.54	7.96±1.77	0.870

*Data are presented as mean \pm SD or n (%)

**Renal artery stenosis < 50%

RAS, Renal artery stenosis; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; CrCl-c; Creatinine clearance corrected for body surface area; CAD, Coronary artery disease; LAD, Left anterior descending; LCX, Left circumflex artery; RCA, Right coronary artery; LVEF, Left ventricular ejection fraction; HbA1c; Hemoglobin A1c

Table 3. Multivariable-adjusted	predictors for renal	atherosclerosis n	resence and extent senarately
Table 5. Multivariable-aujusteu	predictors for renar	ameroscierosis pi	reserved and extern separatery

Predictors	Presence of RAS		Extent of RAS	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (y)	1.03 (1.02-1.05)	< 0.0001	1.04 (1.02-1.05)	<0.0001
Male sex	0.60 (0.44-0.82)	0.0039	0.58 (0.43-0.78)	0.0004
Hypertension	1.67 (1.13-2.47)	0.0005	1.62 (1.11-2.38)	0.0129
History of RF	1.82 (1.22-2.70)	0.0064	1.82 (1.26-2.64)	0.0015
LAD vessel disease	1.67 (1.14-2.45)	0.0081	1.52 (1.03-2.26)	0.0345
LCX vessel disease	2.04 (1.45-2.88)	< 0.0001	1.61 (1.11-2.32)	0.0113
Gensini score	-	-	1.00 (1.00-1.01)	0.0392

RAS, Renal artery stenosis; OR, Odds ratio; CI, Confidence interval; RF, Renal failure; LAD, Left anterior descending; LCX, Left circumflex

angiography in conjunction with coronary angiography (mean age \pm SD: 63.06 \pm 10.32, ranging from 24 to 89 years), 454 (57%) were men. A total of 345 (39.8%) cases had significant ARAS, 77 (22.3%) of which were bilateral. On coronary angiography, 9.1% had normal coronary arteries and 11.8% had minimal coronary artery disease. One-vessel, two-vessel, and three-vessel disease were detected in 17.7%, 19.1%, and 42.4% of the patients, respectively. The baseline clinical characteristics of the studied patients according to the presence and extent of ARAS are presented in Table 1. Patients with ARAS were older, more hypertensive, and more likely to have a previous history of myocardial infarction, cerebrovascular accident, renal failure, and hemodialysis. They also more commonly received insulin therapy. Patients without ARAS (n = 521) as compared to patients with uni- or bilateral RAS (n = 345) had statistically similar BMI (28.14 ± 4.94 vs. 27.74 ± 4.88 , p value = 0.204) (not shown in Table 1).

Table 2 shows that unsurprisingly, the serum level of creatinine was significantly greater in the ARAS group than that in the No ARAS group, while the opposite was true for creatinine clearance. Although the involvement of the left main did not differ between the groups, significant ARAS was more frequently seen in the patients with three-vessel disease or in those with the involvement of each main coronary artery. Severity of CAD, reflected by the Gensini

score, was also higher in the ARAS group than in those without significant renal stenosis. Moreover, there was a strongly significant linear trend of higher Gensini score with increasing ARAS extent - from No ARAS to unilateral and from unilateral to bilateral RAS - (p value < 0.001 for the Mantel-Hanzel Test of Linear Trend).

In the multivariable logistic regression model, using significant ARAS as the dependent variable, six variables were identified as the independent predictors significantly associated with the presence of ARAS, namely age, female sex (male sex was found to be a protector), hypertension, history of renal failure, LAD stenosis > 50%, and LCX stenosis > 50% (Table 3). The predictive performance of the risk model assessed by using the area under the ROC curve (AUC) was good (c = 0.7). Because Hosmer-Lemeshow p value was 0.52 (p value < 0.05 indicates a poor fit), the model was also found to fit the data well. As can be seen in Table 3, according to the Proportional Odds model, the Gensini score was more likely to be associated with a trend towards more extensive ARAS (adjusted OR = 1.00, 95% CI = 1.00-1.01; p value = 0.039). The other independent determinants of the ARAS extent were the same as the predictors of the ARAS presence.

Discussion

In the present study, we investigated patients undergoing simultaneous coronary and renal angiography and found that angiographically evident ARAS (defined as lumen occlusion $\geq 50\%$) was common (near 40%) in this group of patients. Moreover, we included clinical and coronary angiographic variables in a multivariable regression model to predict ARAS in the studied patients. Six variables, i.e. age, female sex, hypertension, history of renal failure, LAD stenosis $\geq 50\%$, and LCX stenosis $\geq 50\%$ were found to be the independent predictors of the ARAS presence. The Gensini sore in addition to the six aforementioned variables constituted the seven independent predictors of the ARAS extent in our study population.

The prevalence of significant ARAS in patients undergoing coronary angiography for suspected CAD has been estimated to range from 3% to near 20%.¹⁸ The high prevalence of ARAS in our study can de explained by the fact that we performed renal angiography mostly in patients with severe or resistant hypertension and renal dysfunction or in those suffering from pulmonary edema with preserved systolic function. This finding is in accordance with that of a previous study examining a contemporary coronary angiography population by using protocol-based patient selection and catheterization.¹⁹

Several previous investigators have suggested that a strong association exists between ARAS and CAD.^{4, 9, 12, 18-24} In a most recent study on 492 consecutive patients

referred for cardiac catheterization, significant two-vessel and three-vessel CAD were found to be strong predictors of the presence of ARAS.¹⁸ We found that the LAD and LCX stenoses were the independent predictors of ARAS, indicating that patients with a combination of the LAD and LCX two-vessel disease as well as patients with threevessel disease are at higher risk for the presence of ARAS. Weber-Mzell et al.9 also found the LAD, LCX, and RCA stenoses to be more frequent in patients with significant ARAS in the uni- but not multivariable analysis. However, they showed that having more extensive coronary lesions was an independent predictor of ARAS. In another study, the LAD disease was univariately more frequent in patients with significant ARAS (defined as stenosis > 75%) but only threevessel disease remained as independent predictor in the multivariable model.¹² The severity of CAD as assessed by the Gensini score was not a predictor of significant ARAS, but it independently predicted the extent of ARAS in our study population.

In line with most of the studies that found older age as an independent predictor of ARAS,^{10, 18, 25, 26} age was strongly and independently associated with ARAS in our study population. In this study, female sex was also significantly associated with ARAS. Wang et al. explained this association by the more advanced age of their female as compared to male patients. It is intriguing that after adjusting for age, CAD severity (by using the Gensini score), and other factors, our multivariable model revealed a strong association between ARAS and female gender, which is of particular interest insofar as CAD burden was greater amongst the male patients. Several previous studies have also shown such a relationship between female gender and the presence of ARAS in multivariable-adjusted models;^{7, 18, 19, 25, 27} this finding remains to be explained.

A significant association was found between hypertension with the presence of ARAS in our study, which is in agreement with numerous prior studies.^{4, 20, 21, 24, 25, 27, 28} However, others have not identified hypertension as a predictor of ARAS.^{7, 12, 18, 29-31} Hypertension has been observed to be both a risk factor and possibly a sign for the activation of renin-angiotensin system secondary to ARAS.²⁷

Although diabetes and hyperlipidemia play an essential role in the pathogenesis of atherosclerosis, in our study, there were no relationships between ARAS and diabetes and hyperlipidemia as well as smoking or family history of CAD. This is in concordance with the results from other similar studies.^{7, 18, 21, 29} Moreover, our univariable analyses showed that insulin use was significantly associated with ARAS but this was not confirmed in the multivariable analysis.

Our data demonstrated that history of renal failure was unsurprisingly independently associated with ARAS. Serum creatinine has been considered a prominent predictor of ARAS in patients undergoing cardiac catheterization in most but not all studies.^{7, 24, 32, 33} Also, two studies have suggested that the severity of renal failure is more related to parenchymal injury than the severity of stenosis.^{34, 35}

The main limitation of the current study was its retrospective cross-sectional design. Another drawback was that the study was conducted in a single center, which may have rendered it biased with respect to patient enrolment. Be that as it may, it is worthy of note that ours is a tertiary referral center admitting patients from across the country. The study was also limited by the absence of protocol-based patient selection. Finally, we did not use quantitative analyses for the severity of CAD or ARAS.

Conclusion

ARAS is prevalent in patients undergoing coronary angiography for suspected CAD. Three-vessel CAD or two-vessel CAD (LAD + LCX) is a powerful predictor of ARAS along with female sex, older age, hypertension, and history of renal failure. The advantage of revascularization over medical therapy for ARAS is still unclear. Although risk versus benefit was not tested in this study, given the progressive nature of ARAS and the need for early detection and intervention, it appears that clinicians could consider renal catheterization in combination with coronary angiography particularly in female patients with advanced age and with significant CAD stenoses in the LAD and LCX.

Acknowledgment

This study was supported by Tehran Heart Center, University of Medical Sciences. We thank Dr. Arash Jalali for the statistical analyses.

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