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Frequency of renal artery stenosis and associated factors in patients undergoing coronary angiography

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ABSTRACT

Background: Coronary artery disease (CAD) is the first cause of mortality in developed and developing countries, including Iran. Identifying high-risk patients can save many from morbidity and mortality. Renal artery stenosis (RAS) seems to be equivalent to CAD in patients with cardiovascular risk.

Objectives: The present study aimed to determine the prevalence, severity, and extent of RAS and its predictors in patients with confirmed CAD on coronary angiography.

Patients and Methods: All patients suspected of ischemic heart disease (IHD), who underwent diagnostic coronary angiography at Heshmat heart hospital, Iran were recruited (May 2015 to June 2016). Patients with confirmed CAD underwent non-selective renal angiography, which was categorized as mild, moderate or severe based on luminal diameter narrowing more than normal >0% to 50%, between 50%-70% and more than 70%, respectively.

Results: Of 233 patients, RAS was observed in 123 (53%). Around 20% were mild, 10% were moderate and 23% were severe. Additionally, RAS in 37% was unilateral and in 16% were bilateral. Besides,19%, 25% and 56% of patients had atherosclerosis in one, two and three vessels, respectively. There was no correlation between the CAD severity and severity of RAS ($P=0.807$).

Conclusions: Higher prevalence of RAS in patients with hyperlipidemia (60% vs. 40%) was detected. Its association with variables affecting CAD indicates that RAS can be a predictor of CAD. Therefore, simultaneous assessment of RAS in coronary angiography can be a good screening method for CAD beside earlier diagnosis of kidney disease.

Implication for health policy/practice/research/medical education:
The aim of this study to determine the prevalence, severity, and extent of RAS and its predictors in patients with confirmed CAD on coronary angiography. So, simultaneous assessment of RAS in coronary angiography can be a good screening method for CAD beside earlier diagnosis of kidney disease.

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Original Article

1. Background

According to reports published by the World Health Organization (WHO), cardiovascular diseases (CVDs) are the first cause of mortality worldwide (1). Identifying the risk factors, predisposing the patient or accompanying CVDs will help to diagnose high-risk cases before cardiovascular accidents occur. Therefore, researchers have tried to identify the risk factors of carotid stenosis, as the main factor, including age, smoking, diabetes mellitus, renal dysfunction, and hypertension (2).

Atherosclerosis is the main cause of stenosis of carotid, coronary, renal, and other arteries (3). On the other hand, renal artery stenosis (RAS) is associated with atherosclerosis in peripheral (4) and coronary arteries (5, 6). Atheromatous RAS is generally asymptomatic and is the major cause of renal hypertension and end-stage renal disease (ESRD) (7,8). Studies have suggested that suspecting RAS in high-risk patients may lead to sooner diagnosis and delayed progression of hypertension and ESRD (9,10). Studies have proven similar risk factors

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for RAS and CVDs, indicating the shared mechanisms. These studies signified higher mortality in coronary artery disease (CAD) patients with associated RAS (11). Due to the significance of CAD, it is therefore logical to include any measurement that would help early diagnosis and management of high-risk cases. Although the evaluation of RAS as a predictor of CAD has not been proven. Moreover, the best diagnostic method for RAS is still controversial. Some studies have considered selective and some non-selective methods, although no studies have compared them. To observe the difference, the nonselective method may be prior due to the better visualization of the renal artery separation from aortal wall (12). The American Heart Association/American College of Cardiology recommends performing renal angiography at the same time as coronary angiography, when patients with CAD have unexplained renal failure, resistant hypertension or multivessel coronary disease.

2.Objectives

We aimed to determine the prevalence, severity, and extent of RAS and its predictors in patients with confirmed CAD on coronary angiography.

3. Patients and Methods

3.1. Study design

In this cross-sectional study, patients who underwent selective diagnostic coronary angiography at Heshmat hospital (May 2014 to June 2015) were enrolled in the study by consecutively using the convenient sampling method. The sample size was calculated to be 247 based on the study by Cohen and colleagues (z_1-$\alpha_{/2}$=1.96, P= 11.7%, and d=0.04). Patients with normal coronary arteries or hemodynamically unstable patients during catheterization were also not included in the study. Patients with confirmed CAD underwent non-selective renal angiography, through the same iodized-contrast injection by right-sided Judkins catheter which was categorized as mild, moderate or severe based on luminal diameter narrowing more than normal >0% to 50%, between 50-70% and more than 70%, respectively.

Serum creatinine was determined before and 48 hours after angiography. Renal dysfunction was defined as 0.3 mg/dL increase in the creatinine level from baseline. In cases of renal dysfunction, patients received normal saline based on their weight and when needed *N*-acetyl-cysteine before angiography. Renal function was carefully monitored after the angiography, to diagnose and treat cases of renal dysfunction. Patients with renal dysfunction were discharged after 48 hours and patients with increasing level of creatinine were hospitalized for 5 or 7 days to evaluate their renal impairment by daily checking of serum levels of creatinine and urea. The evaluation was performed one day before the procedure and three days after coronary angiography. Glomerular filtration rate (GFR) was estimated by MDRD formula (Modification of Diet in Renal Disease). For prevention of nephropathy induced by iodinated contrast, patients who had estimated GFR (eGRF) below 60 mL/min/m^2 received normal saline infusion (1 mL/kg/h) before and 24 hours after the procedure plus 600 mg oral *N*-acetyl-cysteine twice daily, and iso-osmolar contrast for the procedure.

Data regarding coronary angiography, such as the number of vessels involved, RAS and left ventricle ejection fraction (LVEF), demographic characteristics, medications, cardiovascular risk factors, medical and family history and other variables such as the level of serum creatinine prior to angiography were collected.

3.2. Ethical approval

The protocol of the study has been approved by the Ethical Committee of Guilan University of Medical Sciences (Approval No. IR.GUMS.REC.1920141902) and performed based on the 1964 Declaration of Helsinki and its later amendments. The design and objectives of the study were explained to all participants and written informed consent was obtained from the participants. The data was kept confidential and anonymous in all phases of the study and the costs of the renal artery angiography were provided by the research team and not imposed on patients. The results of both angiographies were explained to the patients.

3.3. Data analysis

The qualitative variables are presented as frequency (percentage) and quantitative variables are presented as mean (standard deviation) or median (range), based on their normality. In the univariate analysis, the logistic regression was used to determine the potential risk factors of the outcomes and all variables associated with the outcome (P< 0.2) were entered in the multivariable model. In the multivariate model, factors that correlated with each other were not entered into the model simultaneously and a backward stepwise method was used for identifying variables that are significantly associated with the outcome. The serum levels of creatinine, potassium, hemoglobin and GFR were grouped based on their quartiles and assessed in the logistic regression model, both continuous and categorized. All statistical tests were two-sided. Statistical analysis was performed using SPSS software, version 19.0 (SPSS Inc, Chicago, IL, USA). P values less than 0.05 were considered statistically significant.

4. Results

We included 233 patients in the study. RAS was observed

in 123 (53%) patients. Around 47 patients (20%) had mild and 23 patients (10%) had moderate and finally 53 patients (23%), had severe RAS, respectively. RAS was unilateral in 85 patients (37%) and bilateral in 38 patients (16%). Patients' demographic characteristics are shown in Table 1.

Prevalence of patients with atherosclerosis in one, two and three vessel(s) was 19%, 25% and 56%, respectively. Distribution of RAS according to the degree/extent of CAD is shown in Table 1 and Figure 1.

There was no relation between the severity of CAD and the severity of RAS ($P=0.807$). Univariate logistic regression analysis showed age, chronic kidney disease (CKD), GFR and categorized serum creatinine were associated with severity of RAS (Table 1). Patients with severe RAS were older, had chronic kidney disease, had also lower GFR and higher levels of serum creatinine (Figures 2, 3, and 4). In multivariable analysis, GFR was the only predictor of RAS more than 70% of stenosis (OR=0.946, 95% CI: 0.926-0.967, $P\leq0.001$).

We also compared the risk factors of atherosclerosis between patients with (luminal diameter narrowing more than normal) and without RAS (normal). In the univariate logistic regression, hyperlipidemia (P=0.002),

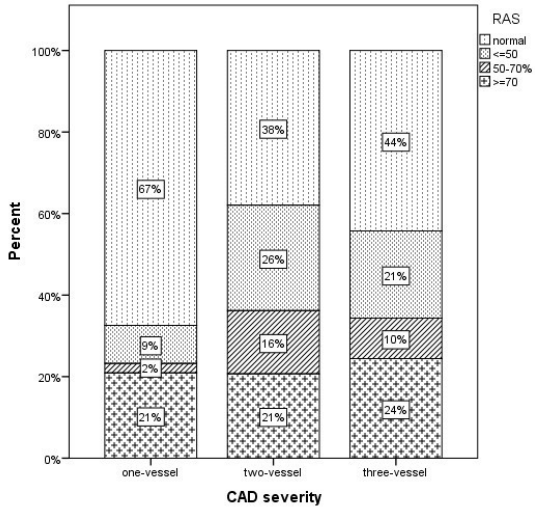

Figure 1. Relationship between CAD severity and prevalence of severe RAS.

CKD ($P=0.025$), three vessels versus single vessel involvement ($P=0.011$), previous MI ($P=0.071$), higher serum creatinine levels ($P=0.023$), lower hemoglobin levels ($P=0.009$) and lower GFR ($P<0.001$) were associated with RAS (luminal diameter narrowing more

Table 1. Patients demographic and clinical characteristics

Characteristics	All patients (n=233)	RAS			*P*
		Mild (n=47, 20%)	Moderate (n=23, 10%)	Severe (n=53, 23%)	
Sex					0.156
Male	103 (44)	21 (45)	15 (65)	19 (36)	
Female	130 (56)	26 (55)	8 (35)	34 (64)	
Age (y), mean (SD)	64 (10)	64 (10)	62 (6)	67 (10)	0.019
Hypertension, yes	179 (77)	34 (72)	17 (74)	41 (77)	0.986
Diabetes mellitus, yes	110 (47)	25 (53)	9 (39)	27 (51)	0.581
Hyperlipidemia, yes	150 (64)	38 (81)	19 (83)	34 (64)	0.892
Previous MI, yes	46 (20)	12 (26)	5 (22)	13 (25)	0.339
CKD, yes	31 (13)	5 (11)	2 (9)	15 (28)	<0.001
Ejection fraction					0.677
≥ 55% normal	103 (44)	22 (47)	12 (52)	21 (40)	
45-55 mild systolic dysfunction	61 (26)	7 (15)	5 (22)	13 (25)	
30-45 moderate systolic dysfunction	59 (26)	15 (32)	5 (22)	16 (30)	
<30 severe systolic dysfunction	9 (4)	3 (6)	1 (4)	3 (6)	
Extent of CAD					0.807
1-Vessel CAD	44 (19)	4 (9)	1 (4)	9 (17)	
2-Vessel CAD	58 (25)	15 (32)	9 (39)	12 (23)	
3-Vessel CAD	131 (56)	28 (59)	13 (57)	32 (60)	
Serum creatinine (mg/dL), median (range)	1.1 (.6-15.6)	1.1 (.7-14.2)	1.2 (.8-13.9)	1.4 (.7-13.1)	<0.001
K, median (range)	4.0 (.8-5.0)	4.0 (3.4-4.9)	3.9 (3.3-4.6)	4.1 (.8-4.9)	0.725
Hemoglubin, median (range)	13.0 (.7-17.2)	12.6 (.7-16.6)	13.6 (1.2-15.7)	12.9 (1.0-17.2)	0.532
GFR, mean (SD)	64 (20)	68 (18)	61 (18)	51 (18)	<0.001

RAS, renal artery stenosis; MI, myocardial infarction; CAD, coronary artery disease; Hb, hemoglobin; OR, odds ratio; CI, confidence interval; SD, standard deviation.

P value was reported from logistic regression and compared patients with severe RAS and others.

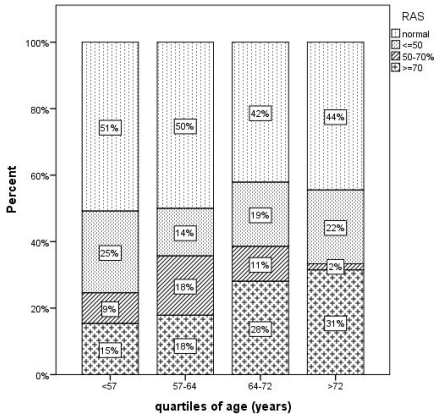

Figure 2. Relationship between age and prevalence of severe RAS.

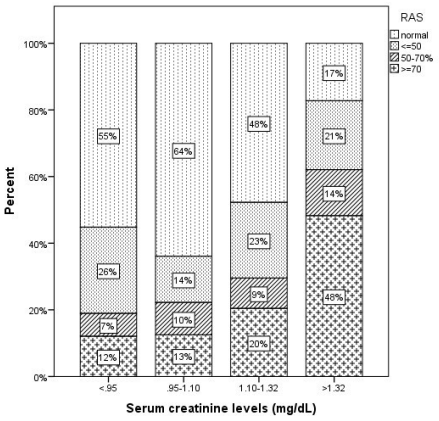

Figure 4. Relationship between serum creatinine and prevalence of severe RAS.

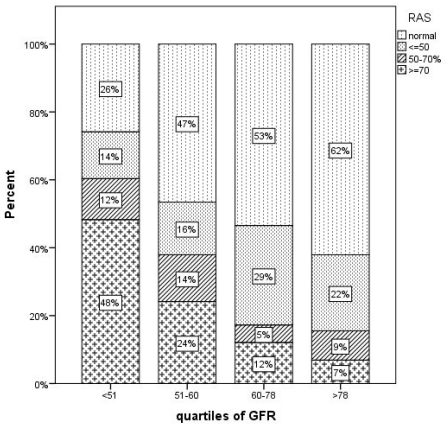

Figure 3. Relationship between GFR and prevalence of severe RAS.

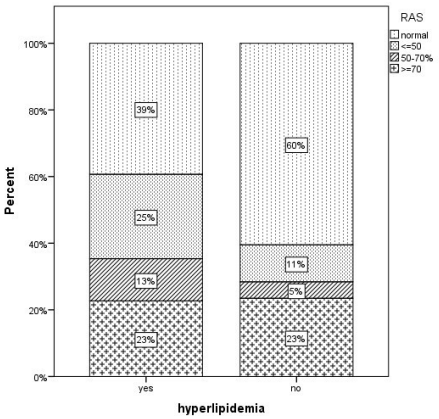

Figure 5. Relationship between hyperlipidemia and prevalence of RAS of any severity.

than normal). However, in multivariable analysis only lower GFR and hyperlipidemia were significantly related with RAS (Table 2).

Prevalence of RAS was 61% in patients with hyperlipidemia compared with 40% in patients without hyperlipidemia (Figure 5).

5. Discussion

The results of the present study indicated that RAS of any severity existed in 53% of patients. Additionally, age, chronic kidney disease, lower GFR and higher levels of serum creatinine were associated with severity of RAS, indicating GFR as the only predictor of RAS>70% stenosis. This finding establishes the higher possibility of ESRD in patients with RAS. RAS has a direct association with low GFR and hyperlipidemia. Following high prevalence of hyperlipidemia and previous myocardial infarction, in RAS patients, it can be concluded that RAS assessment is a good diagnostic tool for subclinical CVDs.

The results of the present study regarding the above-mentioned points are in agreement with other studies (5,9,13). Zanoli and colleagues have followed 181 patients for 4.5 years and have reported higher risk of cardiovascular events in low-to-moderate RAS and have introduced minimal diameter a better prognostic factor for CVD than the percentage of stenosis (14). Bageacu et al assessed 450 patients undergoing coronary angiography and detected RAS and visceral artery stenosis in females older than 60 of high diagnostic value (15). Their results

Table 2. Independent predictors of RAS for any severity (model 1) and severe RAS (model 2) from the multivariable logistic regression analysis

Characteristics	OR	95% CI	P
Model 1			
GFR	0.976	0.963-0.990	0.001
Hyperlipidemia, yes	2.345	1.326-4.147	0.003
Model 2			
GFR	0 .946	0.926-0.967	<0.001

P value of the Hosmer-Leme shows that goodness of fit test was 0.938 and 0.883 for model 1 and 2, respectively.

regarding association of higher age and RAS to CAD is in line with our study, although they have defined RAS as stenosis of higher than 50%. Moreover, they reported a 10% incidence of RAS in patients with established CAD, which was much lower than the present study. Cohen and colleagues also reported 11.7% more in the prevalence of RAS among patients undergoing coronary angiography (16). The difference in the prevalence of RAS can be due to the difference in inclusion criteria of patients (non-selective angiography), and the difference in demographic characteristics of patients (such as age) and different definitions of RAS.

Sen et al evaluated 95 patients undergoing coronary angiography in two groups with and without RAS. They found significantly higher age, dyslipidemia, and higher single-vessel disease in the group with RAS (17), which was similar to the results of the present study. Yet, there is no consensus on the association of gender with RAS; on the other hand, the present study showed no significant difference of gender with RAS, while Sen et al and Olivier et al showed male dominancy (13, 17). In contrast, Islam et al and Cohen et al found female dominancy (16, 18). Diabetes mellitus was also significantly associated with RAS in some studies (14, 17) and not in some others (15, 16) including ours.

Animal studies have confirmed an interaction between mild myocardial ischemia and renal stenosis beyond systemic atherosclerosis, which might be due to increased kidney oxidative stress, inflammation, and fibrosis (19). As far as such studies are only possible in animal models, the mechanism of this association should be further investigated in large-scale cohort studies, randomized clinical trials, or on human autopsies.

As the strengths of the present study, our investigation includes a wide range of variables, enabling a wide view for physicians and researchers.

The results of the current study suggest that cardiologists should alter their traditional look on the risk factors of CVDs and use novel diagnostic methods, including RAS, to diagnose and treat the subclinical cases of cardiovascular and renal diseases, which will highly affect the total mortality and morbidity rate of the society.

6. Conclusions

Higher prevalence of RAS in patients with hyperlipidemia (60% versus 40%) and its association with variables affecting CAD, including vessel involvement, and previous myocardial infarction indicates that assessing RAS can be a predictor of CAD. The present study showed no significant association of gender with RAS. Additionally, diabetes mellitus has no significantly associated with RAS in our study. Therefore, simultaneous assessment of RAS in coronary angiography can be a good screening method for CAD beside earlier diagnosis of kidney disease.

Limitations of the study

It had some limitations including lack of follow-up of patients, which would demonstrate long-term cardiac and renal outcomes, but was beyond the objectives of the present study due to the cross-sectional nature of the study.

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Authors' contribution

FM, AS and MGH contributed to study design, preparation of manuscript and final revision. FM and MM participated in data gathering. AA conducted data analysis and interpretation. All authors read and approved the paper.

Conflicts of interest

All authors declare no potential conflicts of interest.

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