Frequency of renal artery stenosis among cohort of Jordanians undergoing drive-by renal angiography at time of conventional cardiac catheterization

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ABSTRACT

الأهداف: تحديد تكرار حدوث تضيق الشريان الكلوي RASعن طريق القسطرة الروتينية في مجموعه من المرضى أثناء أجراء عملية القسطرة الشرايين الاكليليه لهم بشكل غير طارئ. أما الهدف الثانوي فقد كان تحديد المتغيرات المحتملة التي يمكن أن تنبئ بتضيق الشريان الكلوي RAS في هذه المجموعة.

الطريقة: كانت هذه دراسة مستقبليه مقطعيه مستعرضه ذات شواهد تم من خلالها إجراء عمليه قسطرة شرايين الكلي بشكل روتيني على(870) مريض متتالي، على هامش إجراء عملية القسطرة الاكليليه لهم. تمت الدراسة في مركز الملكة علياء لأمراض وجراحة القلب خلال مدة 4 شهور خلال الفترة من 1/1/2006 إلى 30/4/2006. يعرف RAS بأنه تضيق القطر يبلغ 50%< في تصوير الأوعية الدموية الاعتيادي. تم تحديد شدة وتضيق الشرايين الكلوية RAS ثم حللت المعلومات تحليلا أحادي المتغيرات وآخر انحداري لوجستي متعدد .

النتائج: تم اكتشاف تضيق الشريان الكلوي RAS في (21) مريض مما يعطي تكرار مقداره 2.4%. باستخدام التحليل أحادي المتغيرات، كان هناك ترابط هام بين تضيق الشريان الكلوي RAS وعدة عوامل هي العمر، الجنس الأنثوي، شدة تصلب الشرايين الإكليلية، ارتفاع التوتر الشرياني الانقباضي، وفحص التخلص من مادة الكرياتينين. أما بعد التحليل الانحداري اللوجستي المتعدد فقد اقتصرت العوامل المنبئة لتضيق الشريان الكلوي RAS على الجنس الأنثوي (p=0.006، CI : 1.73–25.31، OR 6.61)، وعلى فحص التخلص من مادة الكرياتينين في الذكور(p=0.004، CI 1.21–3.67، OR 1.97).

خاتمة: تم ملاحظة معدل تكرار منخفض لتضيق الشريان الكلوي RAS في هذه الدراسة. أن إجراء تلوين شرايين الكلى على هامش تلوين الشرايين الاكليليه هو غير مبرر في المرضى الأردنيين إلا في أولائك ذوي عوامل الخطورة العالية لحدوث هذا التضيق.

Objectives: To determine the frequency of renal artery stenosis (RAS) by performing routine renal angiography in a cohort of patients undergoing clinically indicated non-emergent coronary angiography. A secondary goal was to define potential variables which may predict RAS in this cohort.

Methods: This was a prospective observational cross-sectional study whereby routine drive-by renal angiography was performed in 870 consecutive patients undergoing non-emergent coronary angiography at Queen Alia Heart Institute, Amman, Jordan during a 4-month period extending from January 2006 to April 2006. Patients were evaluated regarding the presence and severity of RAS. Renal artery stenosis has been defined as diameter stenosis >50% on conventional angiography. Univariate analysis and multivariate analysis were then performed to evaluate potential predictors for RAS.

Results: Renal artery stenosis was found in 21 patients leading to a very low frequency of 2.4%. In univariate analysis, significant association with RAS was found with age, female gender, coronary artery disease severity, systolic blood pressure and creatinine clearance. In multivariate analysis, the only significant predictors were female gender (odds ratio 6.61, confidence interval 1.73-25.31, and p=0.006) and creatinine clearance in males (odds ratio 1.97, confidence interval 1.21-3.67, p=0.004).

Conclusion: Low frequency of RAS was noticed in our study. Performing drive-by renal angiography may be not justified in Jordanians except in high risk subgroups for RAS.

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Atherosclerotic renal artery stenosis (RAS) is the most common cause of secondary hypertension, being present to some degree in less than 5% of the general population of hypertensive patient.[1] However, in several clinical subsets of patients this percentage of association increases to affect up to 11-23% of patients undergoing angiography for suspected coronary artery disease (CAD),[2-6] 24% of patients with renal insufficiency[7,8] and up to 28% in patients with occlusive peripheral vascular disease.[9] In long term follow up of a cardiac catheterization population, RAS was found to be correlated to mortality. The increase in mortality is directly related to the severity of RAS. The more severe the stenosis, the higher the mortality risk.[10] The presence of bilateral RAS significantly reduced 4-year survival in affected patients to 47% compared with 59% (p<0.001) in patients with unilateral RAS.[11] In our cardiology practice at Queen Alia Heart Institute (QAHI), as in many cardiac centers worldwide, screening renal angiography is routinely performed in all patients undergoing cardiac catheterization for suspected atherosclerotic heart disease since 2001. The real frequency of RAS in Jordanians with suspected CAD was never determined and in view of the several potential complications that can follow the performance of renal angiography procedures, we decided to undertake this study to determine the frequency of RAS in a cohort of Jordanian patients undergoing cardiac catheterization for suspected CAD. A secondary goal was to define variables, which may predict RAS in the same cohort. Both goals would help to determine whether to continue adopting the strategy of routine drive-by renal angiography in our cardiac catheterization laboratory or not.

Methods. Routine selective or nonselective drive-by renal angiography was performed in 870 consecutive patients (586 males, 284 females) undergoing non-emergent coronary angiography for 2 cardiology teams at QAHI during a 4-month period extending from January 2006 to April 2006. A written informed consent was obtained from each patient before the procedure. The local ethical committee of Royal Medical Services approved the study. Selective angiography used a right Judkins coronary catheter with hand injection of contrast agent in each main renal artery. Nonselective angiography was performed using pigtail catheter and injector as shown in **Figures 1a & 1b**.

All patients with suspected CAD who were scheduled for coronary catheterization were included in the study including those with clinical or radiographic evidence of previous stroke, transient ischemic attack, carotid artery disease and peripheral vascular disease. Exclusion criteria included patients with a serum creatinine level greater than 2.5 mg/dL because of potential safety concerns about contrast volume administration, patients who underwent renal angiography during the last one year to avoid unnecessary angiography repetition, patients with familial medial degeneration and patients with prior history for renal revascularization or nephrectomy.

Patients were evaluated regarding the presence and severity of RAS based on separate visual estimation of angiograms by 2 senior cardiologists. Renal arteries were categorized as normal, mildly diseased 20-49%, moderately stenotic 50-69%, and severely stenotic 70-99%. Renal artery stenosis has been defined as diameter stenosis >50% on conventional angiography.[3] Creatinine clearance was estimated from the plasma creatinine concentration (PCr), gender, age, and body weight of the patient using the Gault-Cockroft formula.[12]

Univariate analysis was performed to evaluate the frequency of RAS according to several pre-determined risk factors including demographic (age, gender, diabetes, systolic blood pressure, diastolic blood pressure, smoking status, and body mass index), clinical (creatinine clearance) as well as angiographic variables (Coronary artery severity, left ventricular ejection fraction). Continuous variables were expressed as mean values ± SD and categorical variables as absolute values and percentages. For the sake of analysis, the 4 groups were recorded into 2 groups; the first defined non-stenosis group (0-20%, 20% to 49% disease), while the second group defined renal stenosis group (≥50% to 69%, ≥70% stenosis), according to the definition previously mentioned. Categorical data (gender, smoking, presence or absence of diabetes or smoking) between the 2 groups were studied using chi-square test, while continuous variables were studied using t-test. Multivariate analysis of significant univariate predictors of RAS was then performed using the block entry method. Differences were considered significant if p value was <0.05. These computations were carried out with the Systat for Windows, version 10 (SPSS Inc).

Results. Eight hundred and seventy patients were studied, 284 females (32.6%) and 586 males (57.4%). In 849 patients (97.6%) no significant RAS was found (non-RAS group), while RAS was found in a total of 21 patients, leading to a very low frequency rate of (2.4%), in comparison to previously reported studies. Baseline characteristics of study population are shown in **Table 1**. Unilateral moderate RAS was found in 7 patients, bilateral moderate RAS was found in 3 patients. Unilateral severe RAS was found in 8 patients and bilateral severe stenosis in 2 patients. One patient had left severe RAS with concomitant right moderate stenosis, as shown in **Table 2**.

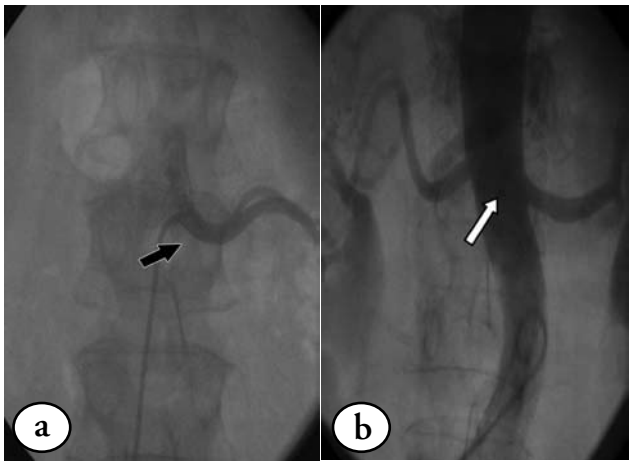

Figure 1 - Non-selective **a)** left-hand-side versus selective **b)** right-handside) renal angiography.

Table 1 - Baseline characteristics of study population , with univariate analysis according to several demographic and clinical variables.

Variables	No RAS (n=849) Normal - 50% disease		RAS (n=21) ≥ 50% disease		*P*-value
Categorial variables	n	(%)	n	(%)	
Female	272	32	12	57	0.005
Smoking status	277	33	9	43	0.17
Presence of HTN	215	25	13	62	0.004
Presence of DM	307	36	11	52	0.312
Continuous variables	Mean ± SD		Mean ± SD		
Age	61 ± 11		68 ± 8		0.04
BMI kg/m^2	26.9 ± 4.2		25.4 ±2.6		0.10
SBP (mm Hg)	134.8 ± 23.1		141.7 ± 25.7		0.007
DBP (mm Hg)	81.7 ± 11.8		80.8 ± 11.1		0.30
Creatcl. males (mL/min/m^2)	79.8 ± 16.8		73.7 ± 15.5		0.002
Creatcl. females (mL/min/m^2)	75.1 ± 13.8		72.4 ± 20.7		0.001

RAS - renal artery stenosis, BMI - body mass index, HTN - systemic hypertension, DM - diabetes mellitus, SBP - systolic blood pressure, DBP - diastolic blood pressure, Creatcl. - creatinine clearance. Probability values were considered significant if <0.05. T-test was used for continuous variables and the Chi-square test for categorical variables.

Table 2 - Results of renal angiography categorized by severity and side of renal artery stenosis.

Results RAS	Left renal artery			
Frequency	Normal	20-49%	50-69%	70 - <99%
Right renal artery				
Normal	744	40	2	3
20-49%	41	24	2	2
50-69%	1	2	3	1
70 - <99%	1	2	0	2

RAS - renal artery stenosis.

Patients with RAS were older, had higher systolic blood pressure, and more often hypertensive. The 2 groups did not differ with respect to smoking status, presence of diabetes, and diastolic blood pressure. The clinical and demographic characteristics of the RAS and non-RAS groups are shown in **Table 1**.

Non-obstructive CAD was present in 464 patients (53.3% of study population, whereas the frequencies of single vessel disease (SVD) (n=206 [23.7%]), 2 vessels (n=145 [16.7%]), 3 vessels (n=45 [5.2%]) and left main disease (LM) (n=10, [0.2%]) (**Table 3**). The frequency of RAS increased with the number of stenotic coronary arteries, starting from 1.1% (5 RAS among 464 patients) in the normal/non-obstructive subgroup, raising up to 2.9% in patients with SVD (6 RAS among 206 patients), to 4.1% in patients with 2 vessels (6 RAS among 145 patients), to 4.4% in patients with 3 vessels (2 RAS among 45 patients), to lastly reach 20% in patients with LM disease (2 RAS among 10 patients). In the univariate analysis, the extent of CAD (p=0.005), but not the left ventricular ejection fraction was significant predictor of RAS (**Table 3**).

Using those variables, which differed significantly between the RAS and non-RAS groups in the univariate analysis, a multivariate analysis was performed using the block entry method. In this model, association did persist only with female gender (odds ratio 6.61, confidence interval: 1.73-25.31, p=0.006) and creatinine clearance in males (odds ratio 1.97, confidence interval: 1.21-3.67, p=0.004), as shown in **Table 4**.

Discussion. Significant silent RAS is a well accepted cause of deterioration of arterial hypertension and of renal insufficiency.[11,13,14] Progression of atherosclerotic stenosis occurs in 10% of patients with RAS regardless of medical therapy to control hypertension.[13,14] Recently, more interest has been focused on the impact of endoluminal renal artery revascularization of RAS compared with medical management on patient survival. Numerous single center studies have reported the beneficial effect of percutaneous transluminal renal angioplasty in terms of better hypertension control, improvement or preservation of renal function and, possibly, an improved survival in patients with CAD referred to revascularization.[15-18] However, none of the so far published or presented randomized controlled trials could prove a beneficial outcome of RAS revascularization compared with medical management. Bax et al[19] recently showed that stent placement with medical treatment had no clear effect on progression of impaired renal function but led to a small number of significant procedure-related complications. They favored a conservative approach to patients with RAS. Similarly, due to the negative results of the recently

Table 3 - Prevalence of renal artery stenosis (RAS) according to angiographic variables.

Variables/category	RAS								P value
	Normal <20%		20- 49%		50- 69%		70- <99%		
LVEF									0.95
<30%	149	(17.1)	19	(2.2)	2	(0.2)	3	(0.3)	
30-50%	220	(25.3)	28	(3.2)	3	(0.3)	3	(0.3)	
Normal	375	(43.1)	58	(6.7)	5	(0.6)	5	(0.6)	
CAD severity									0.005
Normal/ <50% plaque	417	(47.9)	42	(4.8)	1	(0.1)	4	(0.5)	
SVD	178	(20.5)	22	(2.5)	4	(0.5)	2	(0.2)	
2VD	113	(12.9)	26	(2.9)	3	(0.3)	3	(0.3)	
3VD	32	(3.7)	11	(1.3)	1	(0.1)	1	(0.1)	
LM	4	(0.5)	4	(0.5)	1	(0.1)	1	(0.1)	

LVEF - left ventricular ejection fraction, CAD - coronary artery disease, SVD - single vessel disease, LM - left main.

Table 4 - Multivariate associations with severe renal artery.

Variable	Odds ratio	95% Confidence interval		*P*-value
		Lower	Upper	
Female gender	6.61	1.73	25.31	0.006
Creatinine clearance in males	1.97	1.21	3.67	0.004

presented ASTRAL trial (The Angioplasty and Stent for Renal Artery Lesions),[20] referrals to endovascular renal artery revascularization decreased. Meanwhile, the results of CORAL trial (Cardiovascular Outcomes in Renal Atherosclerotic Lesions),[21] the largest trial conducted by National Institutes of Health-funded programs in this regard, are eagerly waited. Regardless of which treatment method is more effective when RAS is discovered, screening for severe RAS is recommended for those with an intermediate absolute risk[22] and is reasonable only in patients at increased risk for RAS who are candidates for revascularization as concluded by the American College of Cardiology/American Heart Association peripheral arterial disease management guidelines.[23] Unfortunately, these guidelines appear ill advised, since their phraseology includes practically every patient with atherosclerosis, and may lead to unjustified increase in percutaneous intervention.[24] Another dilemma, in fact, is the search for the already mentioned high-risk predictors. Although many trials from different parts of the world demonstrated independent correlation of significant RAS with hypertension,[5,6,25-27] stroke and/or, carotid and/or peripheral vascular disease,[5,25 27] CAD,[5,6,26,27] and creatinine clearanc;[5,6,27] however, these variables were inconsistent among different trials. The inconsistency in defining a hemodynamically relevant stenosis among various trials, which was defined as either diameter stenosis is >50% or 70%, further add to the complexity in comparing data. To overcome these differences, Cohen et al[28] suggested that a simple score that can predict the presence of significant RAS among patients referred for cardiac catheterization depending on the following independent predictors ; age, higher creatinine levels, peripheral vascular disease, number of cardiovascular drugs, hypertension, female gender, and 3-vessel coronary artery disease or previous coronary artery bypass graft. In a series of 297 patients with hypertension undergoing coronary arteriography and concurrent abdominal aortography, no patients experienced deterioration in renal function, clinical atheromatous embolization, or prolongation in the length of hospital stay.[25] Abdominal aortography does add cost to the coronary angiographic procedure, but it is comparable to the cost of the noninvasive imaging test that it replaces.[29] However, it is generally accepted that quantitative renal angiography and even color duplex ultrasound derived indices of RAS severity, overestimate the actual severity of RAS. This 'overdiagnosis' is likely the main cause of the disappointing results of renal angioplasty for renovascular hypertension. A ratio of distal renal pressure to aortic pressure (P(d)/P(a)) <0.90 was considered a threshold for defining a significant RAS by Drieghe et al.[30] Determining pressure gradient compare well with diameter stenosis[31] and can predict hypertension improvement after stenting.[32] Univariate analysis in our trial which was performed solely in Jordanian patients, revealed significant association between RAS 50% and age, female gender, CAD severity, SBP and creatinine clearance which is in keeping with the previously mentioned trials;[5,6,17,22-24] however, in multivariate model, our data suggested that RAS could be predicted through the assessment of only 2 variables; female gender (OR 6.61, CI 1.73-25.31, p=0.006) and creatinine clearance in males (OR 1.97, CI 1.21- 3.67, p=0.004). Although the association of CAD severity and RAS prevalence is important, we showed that other clinical variables have a stronger association with RAS.

Taking the very low frequency of RAS in our series and the lack of persistence of association between many recognizable risk factors and RAS in the multivariate model, we would strongly discourage performing drive-by renal angiography in all patients at time of conventional cardiac catheterization. Renal artery stenosis was found only in a total of 21 patients, leading to a very low frequency rate of (2.4%) in our unselected cohort, well below the average frequencies reported in previous trials.[2-6] When the frequency of RAS is low in a certain group of population, the risk versus the benefit of performing screening renal angiography in tandem with diagnostic coronary arteriography must be considered, especially if it is to be performed selectively. Selective angiography entails certainly higher complications when compared to non-selective abdominal arteriography.[25,29] Furthermore, patients who are discovered to have RAS by drive-by angiography are often offered angioplasty even when they do not have signs and symptoms attributable to the presence of RAS. The risk of clinically significant complications following percutaneous balloon angioplasty of renal arteries is in the range of 5-15%, including most prominently the consequences of atheroembolism.[33] Suggested reasons for the low frequency rate of RAS in our trial, may be related to the lower frequency of hypertension and severe CAD in our series. Only 25% were hypertensive while severe CAD ≥1 VD was present in 46.7 % of patients. Harding et al[3] and Park et al[5] reported frequencies of 15% and 10.8% for RAS respectively, in similar study designs, However, the frequency of hypertension and severe CAD among their population were >50% and 66%. Jordan is one of the Mediterranean countries where the use of olive oil and Mediterranean diet is prevalent. So, one of the possible explanations of low RAS frequency may be related to this consumption. Experimental and epidemiological studies have demonstrated the beneficial effects of the traditional Mediterranean diet on the incidence and progression of atherosclerosis, which is also known to lower blood sugar levels and blood pressure. The people living in Mediterranean countries tend to consume relatively high amounts of fat; they have far lower rates of cardiovascular disease than in countries like the United States, where similar levels of fat consumption are found. Llorente-Cortes et al,[34] showed that the Mediterranean diet influences expression of key genes involved in vascular inflammation, foam cell formation and thrombosis. Dietary intervention can thus actively modulate the expression of pro-atherothrombotic genes even in a high-risk population. Genetic factors leading to lower degree of atherosclerosis in Jordanians are another possibility, however, this remains a remote one. How can this be investigated in the context of the last trial, thus, further future investigations are still needed.

Our study is limited because of its dependency on the accuracy of cine abdominal aortography performed in single view for determining the absence or presence of RAS. Previous studies using the AP projection have demonstrated that ostial lesions may be missed in this projection.[35] It is therefore, possible that the true prevalence of RAS is somewhat greater than the reported 2.4%. Unfortunately, borderline lesions were never checked by pressure wires to delineate whether they are significant or not.

In conclusion, we would strongly discourage performing routine drive-by renal angiography at time of conventional cardiac catheterization, taking the lower RAS frequency in our population. Therefore, it is sensible to rest the decision to perform renal angiography at the time of cardiac catheterization only in patients at increased risk of RAS.

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