

Prevalence of Renal Artery Stenosis in 1,656 Patients who Have Undergone Cardiac Catheterization

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OBJECTIVE

To determine the prevalence of renal artery stenosis (RAS) in patients who have undergone cineangiocoronariography.

METHODS

Prospective study of cineangiocoronariography and aortography examinations conducted between January 2002 and February 2004 on 1,656 hypertensive and normotensive patients who underwent the examinations to confirm the diagnosis of obstructive coronary artery disease or valve disease.

RESULTS

The average age of the 1,656 patients was 61.6 ± 11.8 years. Eight hundred and ninety-one (53.8%) were male, 169 (10.2%) were diabetic and 1,054 (63.8%) presented obstructive coronary artery disease. Renal stenosis greater than 50% was observed in 228 (13.8%) patients, and 25 (1.5%) had bilateral stenosis. Obstructive coronary artery disease was defined as stenosis greater than or equal to 50% of the vessel lumen, in one, two or three main arteries, classified as single, double or triple vessels, respectively. Quantification was conducted using visual analysis of the angiography. Comparison of the groups with and without renal artery obstruction $\geq 50\%$, revealed significant statistical differences in relation to gender, age, diabetes mellitus, blood pressure and left ventricular function. However, no statistical difference was noted in relation to the occurrence of coronary artery obstructions $\geq 50\%$. Nevertheless, renal artery obstructions $\geq 70\%$, revealed significant differences in relation to blood pressure, coronary artery obstructions $\geq 50\%$ and left ventricular function, which were all higher in the renal artery obstruction group.

CONCLUSION

The prevalence of RAS found in our study was comparable to that reported by major medical literature case studies. RAS is associated with systemic hypertension (SH), end-stage renal disease (ESRD) and its sequelae, emphasizing how important it is that we are aware of possible candidates for angiographic diagnosis of this disease.

KEY WORDS

Renal artery stenosis, atherosclerosis, end-stage kidney disease, systemic hypertension, angiography with contrast medium.

Primary renal artery diseases generally involve the main artery trunks while secondary diseases are characterized by intrarenal vascular disease and small vessel diseases. The most common etiologies of primary renal artery obstructions are atherosclerosis and fibromuscular dysplasia.

It is estimated that in 1999, in the United States, 344 thousand patients were treated for end-stage renal disease (ESRD) and that roughly 67 thousand others died from this disease. This corresponds to a three year mortality rate close to 50%, which is comparable to the prognosis for lung cancer and class III or IV congestive heart failure (CHF).^{1,2}

Renovascular atherosclerosis is the primary disease for approximately 6% of the ESRD patients that begin dialysis programs³. Additionally, renal artery stenosis (RAS) is presumed to be the etiology for 14%-20% of dialysis patients over age fifty^{4,5}.

More than one third of the patients with RAS greater than 60% have concomitant kidney size reduction of 1 cm or more⁶, a condition known as ischemic nephropathy which obstructs renal blood flow causing ischemia and renal dysfunction.

RAS is also the most common cause of secondary systemic hypertension (SH) corresponding to 5% of all SH cases. This is relevant since SH is a major public health problem with sequelae in various organs and systems as well as a contributing cause of death.

The cumulative two year survival rate for patients diagnosed with unilateral renal artery stenosis is 96%, for bilateral stenosis it is 74%, and for bilateral stenosis with one or both renal arteries occluded it is 47%⁷.

Consequently, there has been a growing interest to identify causes possible of prevention or reversal of SH and renal failure. The reversal of anatomic obstructions in the renal arteries is a promising therapeutic strategy.

Based on this, the objective of this study is to determine the prevalence of atherosclerotic renal disease by means of an angiography study in a population referred by their doctors to have a cineangiocoronariography at a specialized regional hospital.

METHODS

Prospective cross-sectional study, conducted between January 2002 and February 2004 at a class II specialty hospital. The patients were indicated for obstructive coronary artery disease assessments which is defined as an obstructive lesion greater than 50% of the vessel lumen on the angiography. Stenosis in main coronary arteries was classified as single vessel for one artery, double vessel for two arteries and triple vessel for three arteries. Ventricular function was analyzed with a left ventriculography using a 30° right anterior oblique projection. The ejection fraction was calculated for all patients based on the Simpson angiography method, using Philips Integris 3000 (Philips, Netherlands) equipment and software. After calculating

the ejection fraction, the left ventricle contractibility was calculated according to the Herman and Gorlin^{8,9} method and classified as normal, akinesia, hypokinesia (minimal, moderate or serious deficit) and dyskinesia. Patients who underwent a cineangiocoronariography for preoperative cardiac surgery evaluation for valve or aortic diseases were also included in the study.

The study population included 1,656 patients who had undergone cineangiocoronariography and retrograde aortography studies using the right or left femoral artery puncture approach and a 10° left anterior oblique projection with digital subtraction. The catheter pigtail was placed 3 cm above the origin of the renal arteries and 20ml of contrast medium was subsequently administered at an infusion rate of 15 ml/s and a pressure of 600 PSI using an infusion pump (Angiomat 600, Cincinnati, USA). When a lesion was detected, selective catheterization of the affected renal artery was performed using a Judkins right coronary catheter, digital subtraction and manual injection of the contrast medium.

The contrast mediums used were Iohexol 300 mg/ml (Amersham Health Limited, China), Ioversol 320 mg/ml (Mallinckrodt Inc, USA) and Diatrizoate 370 mg/ml (Berlimed, Spain). The contrast medium was chosen by the operator according to previous history of renal dysfunction, diabetes, congestive heart failure functional class III/IV and volume of contrast used. No differences were reported in relation to the three contrast media used.

Significant stenosis was classified as an obstruction greater than 50% of the vessel lumen which was assessed by the visual analysis of the same operator during the diagnostic examination and the later analysis of the relevant angiographic data.

Nondiagnostic aortographies were not considered since whenever some degree of lesion was observed during the aortography, selective catheterization of the renal artery was performed. The patients gave their verbal consent after being informed that an additional small dosage of radiological contrast medium would be used during their procedure which would minimally increase the risk involved.

The data were stored in EpiInfo (CDC/WHO, 2001), version 6.04d, using the program ENTER, and analyzed later with SPSS (SPSS Inc., 2002) version 11.5. Continuous variables were presented as mean \pm standard deviation and categorical variables as absolute numbers (percentages).

RESULTS

The average age of the 1,656 patients was 61.6 \pm 11.8 years. Eight hundred and ninety-one (53.8%) were male, 169 (10.2%) were diabetic, 1,199 (72.4%) had an average systolic blood pressure higher than 140 mmHg during the examination, 1,054 (63.8%) presented obstructive coronary artery disease. One thousand two hundred and thirty patients (74.3%) presented left

ventricle contractile alterations. Renal stenosis greater than or equal to 50% was observed in 228 patients (13.8%) (fig. 1 and 2), and 25 patients (1.5%) had bilateral stenosis. Renal stenosis $\geq 70\%$ was observed in 58 patients (3.5%) of which ten (0.6%) had total artery occlusions. Table 1 shows the differences between the groups with and without RAS $\geq 50\%$ demonstrating the significant statistical differences in regard to gender, age, diabetes mellitus, blood pressure and left ventricular function. Nevertheless, no significant difference was found in regard to the occurrence of coronary artery obstructions $\geq 50\%$. Table 2 shows the differences between the groups with and without RAS $\geq 70\%$, demonstrating the significant statistical differences in regard to blood pressure, left ventricular function and the occurrence of coronary artery obstructions $\geq 50\%$. Since the patients included in the study had originally been referred for a cineangiogram, creatine serum levels were not determined before or after the procedure.

No complications such as thrombosis, dissections or macroembolizations of the renal arteries, aorta or aorta branches occurred during the aortography or selective angiography. Possible renal function alterations or late complications as a result of the procedure were not reported by the patients or attending doctors.

DISCUSSION

The risk of cardiovascular events in adults is more dependent on the degree of hypertension than the cause. The reduction in renal perfusion pressure activates the renin-angiotensin system leading to the release of renin and the production of angiotensin II which is directly related to reduced sodium excretion, increased sympathetic nerve activity, reduced concentrations of intra-renal prostaglandins and the production of nitric oxide causing renovascular hypertension^{10,11}. When hypertension is sustained, plasma renin activity is decreased (referred to as reverse tachyphylaxis), partially explaining the limitations of renin measurements to identify patients with renovascular hypertension.

Blood flow in the kidneys is three to five times higher than in the heart or liver due to the high glomerular capillary filtration requirement. In the presence of lesions that obstruct blood flow, the renal perfusion autoregulatory mechanism produces adaptations in the glomerular vascular resistance of the afferent and efferent arterioles. This compensatory

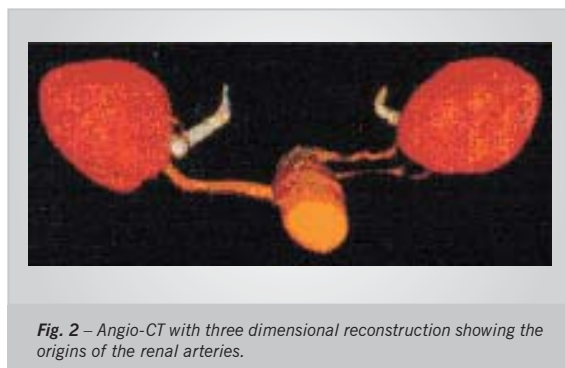
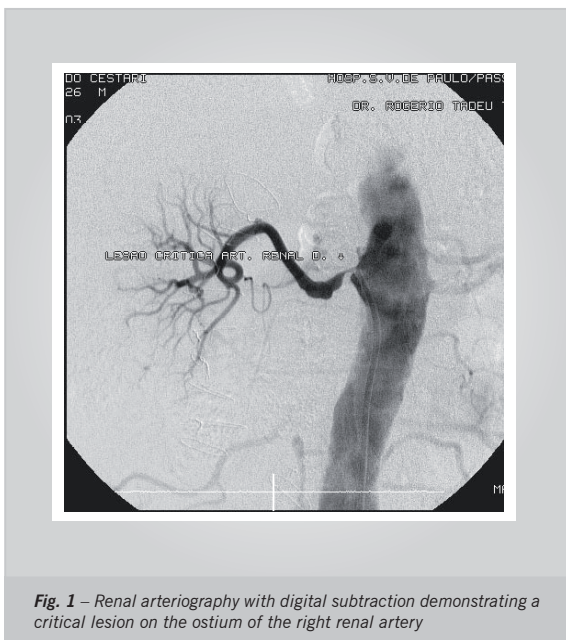


Table 1 – Comparison between the groups with and without renal stenosis $\geq 50\%$

Variable	Global (n = 1656)	Renal Obstruction $\geq 50\%$		p
		Yes (n = 228)	No (n = 1.428)	
Mean age	61.6 \pm 11.8	66.4 \pm 11.6	61.5 \pm 29.4	0.01
Females	765 (46.2%)	132 (58.0%)	646 (45.2%)	<0.001
Diabetes mellitus	169 (10.2%)	37 (16.0%)	131 (9.2%)	<0.01
Systolic BP	146.7 \pm 26.5	163.2 \pm 30.7	144.5 \pm 25.1	<0.001
Diastolic BP	82.5 \pm 16.6	88.4 \pm 19.5	81.8 \pm 16.1	<0.001
Mean BP	103.6 \pm 16.8	113.2 \pm 17.0	102.3 \pm 16.4	<0.001
LV dysfunction	1.129 (68.2%)	139 (61.0%)	990 (69.3%)	0.01
Coronary obstruction $\geq 50\%$	1054 (63.8%)	110 (48.5%)	657 (46.0%)	NS

BP: blood pressure; LV: left ventricle.

Table 2 – Comparison between the groups with and without renal stenosis ≥ 70%

Variable	Global (n = 1656)	Renal Obstruction ≥ 70%		p
		Yes (n = 58)	No (n = 1.598)	
Mean age	61.6 ± 11.8	67.4 ± 10.9	62.0 ± 28.1	NS
Females	765 (46.2%)	27 (46.6%)	751(47.0%)	NS
Diabetes mellitus	169 (10.2%)	10 (17.2%)	158 (9.9%)	NS
Systolic BP	146.7 ± 26.5	165.5 ± 31.4	146.7 ± 25.9	<0.01
Diastolic BP	82.5 ± 16.6	89.0 ± 16.3	82.2 ± 16.6	<0.01
Mean BP	103.6 ± 16.8	115.5 ± 14.3	103.0 ± 16.7	<0.01
LV dysfunction	1129 (68.2%)	53 (91.2%)	1.077 (67.4%)	<0.01
Coronary obstruction ≥ 50%	1054 (63.8%)	44 (75.9%)	724 (45.3%)	<0.01

BP: blood pressure; LV: left ventricle.

mechanism begins to fail when renal perfusion pressure drops below 70-85 mmHg and usually corresponds to renal artery stenosis greater than 70%^{12,13}. In addition, factors such as low shear stress levels and reduced nitric oxide production, increased endothelin production and activation of the renin-angiotensin system can cause localized ischemia, tubular injury, epithelial cell rupture and interstitial fibrosis, resulting in ischemic nephropathy. Renal dysfunction is less common in fibromuscular dysplasia than in atherosclerotic RAS, suggesting that atherogenic factors contribute to more severe renal damage.

Even though renovascular hypertension contributes to malignant or accelerated hypertension it is not immediately distinguished from essential SH. Certain standard findings such as hypokalemia, abdominal bruits, no family history of essential SH, SH with a duration of less than one year, onset of SH after age fifty and SH refractory to clinical treatment are more indicative of renovascular hypertension than other types of SH; however, the predictive values of these conditions are low. In fact, most hypertensive patients with RAS have essential hypertension as indicated by the fact that even after a successful revascularization procedure, SH generally persists. RAS can be isolated or can be associated with systemic hypertension (SH), renal failure (ischemic nephropathy) or both.

Atherosclerosis is responsible for 90% of the cases of renal artery stenosis and generally involves the ostium and proximal third of the main renal artery and perirenal aorta. In advanced cases, diffuse or segmental intrarenal atherosclerosis may also be seen, particularly in patients with ischemic nephropathy. The prevalence of atherosclerotic RAS increases with age, mainly in patients with diabetes mellitus, aortoiliac occlusive disease, coronary artery disease and SH.¹⁴⁻¹⁷

In patients with atherosclerotic RAS, progressive stenosis was reported in 51% of the renal arteries five years after the diagnosis (including 18% of the vessels that were initially normal),^{18,19} 3-16% of the arteries were totally blocked^{15,16,18,19}, and renal atrophy developed in 21% of the patients with RAS greater than 60%.

The etiology of fibromuscular dysplasia accounts for less than 10% of renal artery stenosis cases and is most common among women between the ages of fifteen and fifty. Contrary to atherosclerotic RAS it rarely causes renal artery occlusions.

Series of consecutive necropsies demonstrated a prevalence of 5% for RAS>50% in patients under 74 years of age, 18% for those between 65 and 75 years, and 42% in those over 82 years²⁰. The incidental discovery of RAS is relatively common^{21,22}, even though renovascular hypertension only affects 1% to 5% of SH patients. A review of 149 aortograms by Dustan and associates²³ revealed that roughly 50% of the patients with RAS >50% did not have SH. Nevertheless, the presence of anatomic RAS does not necessarily establish that the SH or renal insufficiency was caused by it. Hansen and associates²⁴ reported a prevalence of 6.8% for renovascular disease in a cohort of 834 young patients, participants in the Cardiovascular Health Study, who underwent renal artery ultrasonography examinations. Aortography examinations, conducted during cardiac catheterization to detect RAS, for 3,987 patients in a 78 month timeframe revealed that 4.8% had RAS >75% and 0.8% had severe bilateral disease²⁵. In a cohort evaluated at Mayo Clinic, the renal arteries of SH patients were studied during cardiac catheterization and revealed a prevalence of 19.2% for RAS >50%, 7% for RAS >70%, and 3.7% for bilateral RAS²⁶.

Patients with an unexplainable progressive or chronic loss of renal function, represent a distinct group and roughly 24% of these patients over age fifty, particularly those with generalized atherosclerosis, recurrent pulmonary edema or uncontrolled SH, could have silent ischemic nephropathy. Ischemic nephropathy is a major cause of ESRD²⁷⁻³⁰. Dialysis patients with renovascular disease have the lowest survival rate (average survival rate of 25 to 34 months) and a five year mortality rate greater than 80%^{27,31-33}.

Patients with clinical findings associated with RAS are indicated for further evaluation (tab. 3). This evaluation can



include non-invasive studies to verify overall renal function such as physiological studies to assess the renin-angiotensin system, perfusion studies to assess the differential renal blood flow and image studies to identify RAS. Owing to the limitations of physiological studies for elderly patients with RAS, image techniques are preferred to identify stenosis in these patients. Duplex ultrasound scans can obtain images of the renal arteries and measure the velocity of flow and wave pressure, but there is a 10%-20% failure rate due to operator inexperience, patient obesity and/or the presence of intestinal gas³⁴. Angio-MRIs and angio-CTs are effective to evaluate renal and aortic circulation but do not enable adequate visualization of distal segments and small accessory arteries^{35,36} (fig. 2).

Invasive evaluation is indicated to confirm the diagnosis and determine the therapeutic plan. It is debatable whether or not it should be conducted in conjunction with the cineangiocoronariography to determine surgical or percutaneous therapeutic planning for patients suspected of having renovascular hypertension, renal dysfunction and diffuse atherosclerosis. Thus the objectives of the angiography with contrast medium are to confirm the diagnosis, determine the renal artery stenosis etiology,

evaluate the extent of the intra-renal vascular disease and verify additional anatomic information such as the presence of accessory renal arteries and associated aneurisms or aorta occlusive diseases.

Low osmolar contrast medium is recommended to minimize injection discomfort but caution should be taken with renal insufficiency patients due to nephrotoxicity. In patients with advanced renal insufficiency the use of nonionic contrast media can diminish the risk of contrast medium-induced nephropathy³⁸.

The prevalence of RAS found in our study was comparable to that reported by major medical literature case studies. Analysis of the group with RAS $\geq 50\%$ revealed a statistical significance in relation to an older age, female gender and diabetes. The RAS group also presented elevated blood pressure levels in relation to the group without lesions. However, this study group did not present a relationship between left ventricular dysfunction and RAS, which can be attributed to coronary artery disease involvement since the objective of the examination was to evaluate the presence of coronary atherosclerosis.

Stratification of the RAS $\geq 70\%$ group revealed a predominance of males while the RAS $\geq 50\%$ group was predominately female, however with no statistical significance. Blood pressure readings were also higher for the patients with renal obstruction $\geq 70\%$. For this group the correlation between left ventricle dysfunction and renal obstructions $\geq 70\%$ or obstructive coronary disease was statistically significant. In relation to age, patients with or without RAS $\geq 50\%$ were in their seventies and those with RAS were on average 4.8 years older (0.9-8.7, CI95%, $p = 0.01$).

Even though there is no documented data, it is estimated that the risk of developing major complications (death, stroke or acute myocardial infarction) during an angiography are similar to a cineangiocoronariography, which is less than 1%.

In conclusion, the association of RAS with coronary artery disease and left ventricle dysfunction emphasizes the necessity of a more extensive approach for atherosclerosis with a detailed investigation, especially for patients in their seventies, due to its systemic manifestation, important clinical relevance due to long term sequelae as well as the known benefits of treatment regarding high systemic blood pressure and renal failure.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Table 3 – Clinical findings associated with renal artery stenosis³⁷
<i>Hypertension</i>
Abrupt onset of hypertension before age fifty (suggestive of fibromuscular dysplasia)
Abrupt onset of hypertension at age fifty or older (suggestive of atherosclerotic RAS)
Malignant or accelerated hypertension
Refractory hypertension (does not respond to therapy with ≥ 3 medications)
<i>Renal abnormalities</i>
Unexplained Uremia (suggestive of atherosclerotic RAS)
Uremia induced by ACE inhibitor treatment
Unilateral decrease in kidney size
Unexplained hypokalemia
<i>Other Findings</i>
Bruits in the abdomen, flanks or both
Severe Retinopathy
Carotid, coronary or peripheral artery disease
Unexplained congestive heart failure or acute pulmonary edema
<i>RAS- renal artery stenosis; ACE- angiotensin-converting enzyme inhibitor.</i>

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