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## Atherosclerotic ischemic renal disease. Diagnosis and prevalence in an hypertensive and/or uremic elderly population

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### Abstract

**Background:** Atherosclerotic ischemic renal disease is a frequent cause of end-stage renal failure leading to dialysis among the elderly; Its prevalence is inferred from autopsy or retrospective arteriographic studies. This study has been conducted on 269 subjects over 50 with hypertension and/or CRF, unrelated to other known causes of renal disease.

**Methods:** All 269 patients were studied either by color-flow duplex sonography (n = 238) or by renal scintigraphy (n = 224), and 199 of the 269 patients were evaluated using both of these techniques. 40 patients, found to have renal artery stenosis (RAS), were subjected to 3D-contrast enhancement Magnetic Resonance Angiography (MRA) and/or Selective Angiography (SA). An additional 23 cases, negative both to scintigraphy and to ultrasound study, underwent renal angiography (MRA and/or SA).

**Results:** Color-duplex sonography, carried out in 238 patients, revealed 49 cases of RAS. MR or SA was carried out in 35 of these 49 patients, and confirmed the diagnosis in 33. Color-duplex sonography showed a PPV value of 94.3% and NPV of 87.0% while renal scintigraphy, carried out in 224 patients, had a PPV of 72.2% and a NPV of 29.4%. Patients with RAS showed a higher degree of renal insufficiency compared to non stenotic patients while there were no differences in proteinuria. RAS, based on color-duplex sonography studies, was present in 11% of patients in the age group 50–59, 18% in the 60–69 and 23% at age 70 and above.

**Conclusions:** A relatively large percentage of the elderly population with renal insufficiency and/or hypertension is affected by RAS and is at risk of developing end-stage renal failure. Color-duplex ultrasonography is a valid routine method of investigation of population at risk for renal artery stenosis.

## Background

Ischemic renal disease is a renal insufficiency associated with main renal artery stenosis or occlusion [1,2]. Chronic ischemia causes progressive renal damage with atrophy and permanent loss of structural integrity. The cause-and-effect relationship between anatomic renal artery disease and renal function is often difficult to establish [3]. Deterioration of renal function derives not only from reduction in blood flow, but also from long term hypertension and concomitant risk factors like diabetes, hyperlipidemia, atheroemboli and aging [4].

Ischemic nephropathy has been recognized in the last decade as a distinct cause of renal insufficiency, especially in patients with advanced age [5]. A substantial percentage of patients with endstage renal failure which requires entering a dialysis program, is primarily affected by ischemic renal disease [6,7]. Estimates of the prevalence of renovascular disease derive mainly from autopsy and angiographic studies of patients with renovascular hypertension or atherosclerotic disease involving other districts of the arterial tree [8–11]. Large population studies based on non invasive diagnostic methods are lacking.

The aim of this study is to evaluate the prevalence of renal artery stenosis in a relatively large population aged 50 and above, with arterial hypertension started over 50 years of age, or with chronic renal failure of late onset not explained by other diagnoses. The study is also aimed at comparing different diagnostic techniques for the detection of renal artery stenosis as well as clinical and biochemical indicators of renovascular disease.

## Methods

This study has been carried out on 269 patients, consecutively referred to the nephrologic outpatient clinic for arterial hypertension and/or chronic renal failure. Patients were selected according to the following criteria: age above 50 years, arterial hypertension starting after this age and/or chronic renal failure of late onset, with or without hypertension and unexplained by other known renal pathologies such as chronic glomerulonephritis, chronic tubulointerstitial disease, polycystic kidneys and obstructive renal disease. Diabetes mellitus was not an exclusion criterion and cases of suspected diabetic nephropathy were included when extrarenal atherosclerotic arterial occlusive disease coexisted. None of the patients was on dialysis treatment or had received a kidney transplantation.

269 patients, 150 males and 119 females, were characterized for clinical and standard biochemical parameters, as reported in Table 1, and subjected to non invasive diagnostic manoeuvres, such as renal radionuclide scintigraphy and color-duplex ultrasonography of renal arteries. In particular, all 269 patients were studied either by color-

flow duplex sonography (n= 238) or by renal scintigraphy (n= 224), and 199 of the 269 patients were evaluated using both of these techniques. 40 of 58 patients who were positive for renal artery stenosis with one or two techniques, underwent renal angiography either with three-dimensional contrast-enhanced Magnetic Resonance Angiography (3D-CE-MRA), and/or with Selective Angiography (SA). 7 of the remaining 18 patients could not be subjected to Magnetic Resonance Angiography because of technical problems (metallic prosthesis or pacemaker); 7 refused the procedure due to claustrophobia. In the remaining 4 cases, renal artery stenosis was on a small kidney. In particular, of 49 patients with a positive ultrasonography, 35 accepted to be submitted to renal angiography, while of 24 patients with a positive scintigraphy, 18 accepted to undergo renal angiography. In addition, 17 patients with negative results for renal artery stenosis with the non invasive manoeuvres, accepted to be submitted to Magnetic Resonance Angiography.

Doppler ultrasonography was carried out after fasting, following a three day of a low fibre diet and without smoking for a minimum of six hours before the procedure. Patients were studied with an Acuson 120 XP/4 (Acuson Corp., Mountain View, CA), equipped with a 3.5 MHz transducer, with longitudinal anterior, lateral and oblique approach, with at least threefold sampling of parameters along the artery. Subjects were asked to lie in the supine position for the study of the abdominal aorta and the origin of the renal arteries. Subsequently patients were turned on either side for the study of the renal arteries at the hilum and of parenchymal perfusion.

Standard criteria for the diagnosis of significant renal artery stenosis ( $\geq 60\%$ ) are [12]: 1. Systolic peak velocity above 180 cm/sec (sensitivity  $\cong 94\%$ , or 98% when peak velocity  $>200$  cm/sec). 2. Renal aortic ratio, defined as the ratio between systolic peak velocity in the renal artery and systolic peak velocity in the abdominal aorta in the suprarenal tract, with a normal value of  $<3.5$ .

Renal radionuclide scintigraphy was performed with a gamma camera (Starcam 4000, General Electric, USA) with  $^{99m}\text{Tc}$ -DTPA (diethylenetriaminepentaacetic acid) in 125 patients and with  $^{99m}\text{Tc}$ -MAG3 (mercaptoacetyltriglycine) in 99 patients, with a total of 224 patients. MAG3 was chosen in patients with creatinine clearance  $<25$  ml/min. Diuretics and/or ACE inhibitors were discontinued at least three days before, if treatment was underway. Criteria of positivity for renal artery stenosis were: Parenchymal transit time  $>4$  minutes; a difference in split renal function  $>30\%$ ;  $T_{\text{max}} >5$  min, with a difference between kidneys  $>1$  min. A captopril test was carried out in 161 patients, by administering captopril 50 mg p.o. one hour before the administration of the tracer. Following captopril

**Table 1: Clinical and laboratory data of the patient population (M ± SD;percent)**

		normal values
Patient, n°	269	
Sex, (M/F)	150/119	
Age, years	65,8 ± 11,9	
Weight, Kg	70,8 ± 11,9	
Creatinine, mg/dl	1,7 ± 1	(0,6–1,2)
Cr. Clearance, ml/min	54,8 ± 30,2	(90–120)
Urea, mg/dl	61,2 ± 33,2	(10–45)
Uric acid, mg/dl	6,5 ± 1,8	(3–7)
Sodium, mEq/L	142 ± 4,3	(136–145)
Potassium, mEq/L	4,6 ± 0,5	(3,6–5)
Cholesterol, mg/dl	243 ± 53	(150–220)
HDL cholesterol, mg/dl	49 ± 13,6	(>45)
Triglycerides, mg/dl	162 ± 83	(50–200)
Urinary protein, mg/24 h	654 ± 1103	(<150)
Systolic BP, mmHg	170 ± 25	(<140)
Diastolic BP, mmHg	96 ± 14	(<90)
Duration of hypertension, years	7,5 ± 6	
	n°	%
Arterial hypertension	238	88,5
Familiar hypertension	113	42,0
Smoking	89	33,0
Diabetes mellitus	42	15,6
Hypertensive retinopathy (stage III and IV) (163/269)	4	2,5
Interventricular septum (154/269)	121	78,5
Stenosis of epiaortic arteries (111/269)	60	54,0
Stenosis of iliofemoral arteries (52/269)	33	63,5
Renal dimensions asymmetry (>11 mm)	135	50,2

administration, criteria of suspected stenosis were: with  $^{99m}\text{Tc-DTPA}$ , a fall in glomerular filtration rate of the affected side >5%; with  $^{99m}\text{Tc-MAG3}$ , an increase of at least 0.15 of the 20 minutes/peak count ratio (ratio between the activity after 20 minutes and peak radioactivity); or a lengthening of >2 min of  $T_{\text{max}}$  value, or a delay of tracer elimination in the pelvis of >2 minutes [13,14].

Magnetic Resonance Angiography was performed with a 1.5 T magnet (Vision Plus; Siemens, Erlangen, Germany) with 25 mT/m gradient strength and 600 microseconds gradient rise time. In all cases a Flash 3D T1-weighted sequence (TR = 4.6; TE = 1.8, FA = 30°, NEX = 1, Slab thickness = 120, FOV = 500, matrix = 200 × 512, n° partitions = 34) was used. The acquisition time of the sequence was 23 s. A phased array body coil was used. Before the acquisition a test bolus was performed (TR = 5.8, TE = 2.4, FA = 10, Thickness = 10, matrix-128 × 256, FOV = 400, NEX = 40), injecting 2 ml of Gd-DTPA at 2 ml/s; in order to establish the correct delay time. The examination was performed administering 0.2 mmol/kg of Gd-DTPA with a power injector (Spectris, Medrad) at a flow rate of 2 ml/s. Images were reconstructed using a standard maximum in-

tensity projection (MIP) algorithm and were reviewed by two radiologists obtaining a final report by consensus. This is a more advanced technique than TOF-MRA (Time of Fly) and PC-MRA (Phase-Contrast), and is especially useful for detection of renal artery stenosis. It is considered to have specificity and sensitivity values approaching selective angiography [15,16].

MR angiography was carried out in a total of 39 patients, 22 with positivity of at least one of the non invasive manoeuvres, and 17 cases with negative results. Selective angiography was carried out in 32 patients among those with at least one positivity for renal artery stenosis, diagnosed with non invasive techniques. Stenosis was considered significant both with MRA and SA when at inspection the reduction in arterial lumen diameter was ≥ 60%. In 14 patients, both MRA and SA were performed. The presence of renal artery stenosis, identified by MRA, was confirmed in all cases by SA. The total number of angiographic studies was 57.

**Table 2: Synopsis of results of non-invasive techniques**

RS	DDS			
	Pos	Neg	Not Tested	All
Pos	22	0	2	24
Neg	27	150	23	200
No tested	0	39	6	45
All	49	189	31	269

**Statistical analysis**

Following a preliminary descriptive analysis, since the available data did not allow to evaluate sensitivity and specificity, contingency tables were created only for evaluation of positive and negative predictive values for the diagnostic techniques. For each index the confidence interval at 95% level was calculated. Mann-Whitney non parametric and Pearson  $\chi^2$  tests were used. Significance threshold level was considered to be  $p < 0.05$ .

**Results**

The number of patients, sex distribution, average age, blood pressure values and several biochemical parameters for the entire population together with other clinical parameters of the population are reported in Table 1.

The population was found to have, on average, a moderate renal insufficiency, as shown by the mean creatinine clearance of  $54.8 \pm 30.2$  ml/min. 88.5% of the patients had arterial hypertension. Hypertensive organ damage was evidenced by a thickening of interventricular septum in 78.5% of cases, revealed by echocardiography. In addition, on average the patients had increased cholesterol levels. Carotid and lower extremities artery stenosis were found in 54% and 63% respectively, of the patients studied. Diabetes mellitus was present in 15.6 %.

A synopsis of the results of the non-invasive techniques is reported in Table 2. Renal color-duplex sonography, performed in 238 patients, showed that 49 (20.6%) were affected by renal artery stenosis. MRA and/or SA were performed in 35 of these 49 patients. The diagnosis was confirmed in 33 cases, while 2 cases were false positive. 23 of 189 patients with a negative result of color-duplex sonography, accepted to undergo a renal angiography. In 20 cases the angiography confirmed the negativity, while 3 cases were found to be false negative. On the basis of these data the positive predictive value of color-duplex sonography was 94.3% (80.8–99.3% Confidence Interval) and the negative predictive value was 87.0% (66.4–97.2% C.I.).

Renal scintigraphy was carried out in 224 patients. 24 patients had a positive test for renal artery stenosis. 18 of 24 patients underwent an angiography. Positivity for renal artery stenosis was confirmed in 13, while 5 cases were false positive. Of 200 cases with negative results, 17 were further examined with angiography; 12 of these cases were false negative. The positive predictive value was 72.2% (46.5–90.3% C.I.), while the negative predictive value was 29.4% (10.3–56.0% C.I.).

The comparison between patients with and without renal artery stenosis (Table 3), based on the results of color-duplex sonography, has shown significant difference in the extent of renal failure. The levels of proteinuria did not reach statistical difference probably due to the groups sizes. Significant difference was also found in the prevalence of renal asymmetry and in percent of patients with diabetes mellitus (Table 3). 59% of the patients had a unilateral stenosis while it was bilateral in 41%. The comparison of renal damage between patients with unilateral and bilateral renal artery stenosis is reported in Table 4.

Renal artery stenosis was found in 11.1% of patients in the 50–59 age group, in 18% in the decade 60–69 and 23% of patients above 70 years of age.

**Discussion**

The primary aim of this study is to evaluate the diagnostic role of the non invasive approach to renal artery stenosis and ischemic nephropathy in the elderly, to compare the clinical and biochemical data of patients with and without ischemic nephropathy and to establish the prevalence of this disease among the selected population in the different decades of life.

Based on a comparison between non invasive techniques such as renal scintigraphy and color-duplex sonography, and the diagnostic gold-standard of arteriography, that is both Magnetic Resonance and/or Selective Angiography, we attempted to assign predictive values to these non invasive techniques. There is sufficient agreement between

**Table 3: Humoral parameters (M ± SD) and percentage of clinical findings in patients with and without renal arterial stenosis**

	with	without	P
Patient, n°	49	189	
Age, years	68,1 ± 8	66,3 ± 8,9	0,18
Creatinine, mg/dl	2,5 ± 1,5	1,6 ± 0,06	<,00001
Cr. Clearance, ml/min	34,7 ± 19,2	58,2 ± 30,8	<,00001
Urea, mg/dl	84 ± 38	57 ± 29	<,00001
Uric acid, mg/dl	6,9 ± 1,8	6,4 ± 1,8	0,07
Sodium, mEq/L	142 ± 4,9	142,2 ± 4	0,6
Potassium, mEq/L	4,6 ± 0,5	4,5 ± 0,4	0,52
Cholesterol, mg/dl	236 ± 58	229 ± 54	0,15
HDL cholesterol, mg/dl	45,6 ± 12	49,6 ± 12	0,06
Triglycerides, mg/dl	176 ± 74	156 ± 76	0,08
Urinary protein, mg/24 h	659 ± 672	595 ± 980	0,14
Systolic BP, mmHg	175 ± 29	166 ± 21	0,07
Diastolic BP, mmHg	93 ± 15	94 ± 13	0,44
	%	%	
Smoking	28,4	31,8	ns
Diabetes mellitus	29,8	13,6	<,01
Hypertensive retinopathy (stage III and IV)	6,1	6,1	ns
Interventricular septum	88,0	74,5	ns
Stenosis of epiaortic arteries	30,0	15,2	ns
Stenosis of iliofemoral arteries	57,1	50,0	ns
Renal dimensions asymmetry (>11 mm)	75,6	43,9	<,001

MRA and SA to combine the outcomes for use as a gold-standard. The good agreement was probably due at least in part to the particular sensitivity and specificity of the MR technique utilized in this study, which is considered superimposable to selective angiography [15–17], at least for the stenosis at the origin or at main renal artery. All our cases tested with both arteriographic techniques had comparable results as far as the presence of renal artery stenosis is concerned. The identity of results has been reported by De Cobelli et al. [18] and by Ghantous et al [15].

There are some limitations in the use of Magnetic Resonance, such as claustrophobia and the presence of pacemakers or metallic prosthesis. Since Magnetic Resonance is generally not employed on a routine basis for screening purposes in large populations due to cost and availability, the less expensive non-invasive imaging techniques should come first in the preselection of affected patients.

In the comparison between color-doppler sonography and radionuclide scintigraphy, unfortunately based on a limited number of patients, the former was apparently clearly superior in terms of positive and negative predictive values, in agreement with data of the literature [19]. However this technique requires an experienced operator in order to reach high levels of reliability. On the other hand, in screening for ischemic nephropathy, among patients with renal insufficiency, radionuclide scintigraphy

was clearly less reliable, either using DTPA or MAG3. This technique may give better results in terms of sensitivity and specificity in a population screened for renovascular hypertension, in general with normal renal function. Scoble et al [19] have underlined that radionuclide scintigraphy may give better results in the screening of renal artery fibrous dysplasia, where hyperreninism is more frequent, while it is of lower diagnostic value in the diagnosis of renal ischemia.

Comparing patients with and without renal artery stenosis in an elderly population, a higher grade of renal insufficiency in patients with renal artery stenosis emerged clearly, whether the stenosis was unilateral (59%) or bilateral (41%). Renal insufficiency was found in both groups (Table 4). Therefore renal artery stenosis in the elderly is associated to atherosclerotic vascular involvement of both kidneys, with bilateral damage to renal function. It is misleadingly simplistic to consider the overall renal damage as deriving from reduced blood perfusion of the kidney, due to renal artery stenosis. The poor correlation existing between the extent of renal artery stenosis and degree of renal insufficiency has been reported previously [3,20]. As for arterial hypertension, no difference was found between stenotic and non stenotic patients (Table 3).

The observation concerning proteinuria is also of interest. The extent of proteinuria did not seem to differ between patients with and without renal artery stenosis, probably

**Table 4: Comparison of renal damage between patients with mono-and bilateral renal arterial stenosis.**

	monolateral	bilateral	P
Creatinine, mg/dl	2,4 ± 1,5	3,0 ± 1,8	0,22
Cr. Clearance, ml/min	41,2 ± 21,9	29,6 ± 16,5	0,15
Urea, mg/dl	76,0 ± 46,4	97,6 ± 36,5	0,08
Urinary protein, mg/24 h	575 ± 627	469 ± 329	0,7

due to the given groups sizes. Therefore the exclusion of patients with proteinuria higher than 500 mg/day from further diagnostic procedures for renal artery stenosis, appears to be unjustified [21,22]. More recently the occurrence of marked proteinuria in patients with ischemic nephropathy has been reported [23,24]. Therefore our data support the hypothesis that atherosclerotic renal involvement may be accompanied by pathologic proteinuria. On the other hand heavy proteinuria is of frequent occurrence in nephroangiosclerosis, focal glomerulosclerosis and cholesterol emboli, conditions found in ischemic nephropathy [25–27] among the elderly.

The data of the medical literature on the prevalence of ischemic renal disease in the elderly are scarce, derived mainly from autoptic findings or from arteriography studies performed for coronary artery disease [7–10]. Our results based on color-duplex ultrasonography findings indicate an elevated occurrence of this disease in this cohort, with an increasing prevalence from the sixth decade, and reaching above 20% after age 70. Therefore the presence of ischemic nephropathy should be considered in elderly patients affected by unexplained renal insufficiency and/or hypertension of late onset. The possible evolution towards further deterioration of renal function in patients with renal artery stenosis and the results of relatively non-invasive renal stenting procedures for prevention and treatment, are indication for an extensive screening of at risk subjects.

**Competing interests**  
None declared

**Authors' contributions**

1. GC conceived and coordinated the study
2. SC clinical work
3. SL expert in DDS
4. EM clinical work and participation in design of the study
5. IN biostatistical work

6. GR carried out renal scintigraphy
7. MR magnetic resonance performance
8. GV collaboration in renal scintigraphy
9. DS clinical laboratory work
10. MF clinical work and assistance in coordination
11. AZ endovascular surgery and selective angiography
12. RC DDS expert

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