Analysis of the Sensitivity and Specificity of Noninvasive Imaging Tests for the Diagnosis of Renal Artery Stenosis

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Abstract

Background: **Aging and atherosclerosis are related to renovascular hypertension in elderly individuals. Regardless of comorbidities, renal artery stenosis is itself an important cause of cardiovascular morbidity and mortality.**

Objective: **To define the sensitivity, specificity, positive predictive value, and negative predictive value of noninvasive imaging tests used in the diagnosis of renal artery stenosis.**

Methods: **In a group of 61 patients recruited, 122 arteries were analized, thus permitting the definition of sensitivity, specificity, and the relative contribution of each imaging study performed (Doppler, scintigraphy and computed tomographic angiography in comparison to renal arteriography).**

Results: **The mean age was 65.43 years (standard deviation: 8.7). Of the variables related to the study population that were compared to arteriography, two correlated with renal artery stenosis, renal dysfunction and triglycerides. The median glomerular filtration rate was 52.8 mL/min/m^2. Doppler showed sensitivity of 82.90%, specificity of 70%, a positive predictive value of 85% and negative predictive value of 66.70%. For tomography, sensitivity was 66.70%, specificity 80%, positive predictive value 87.50% and negative predictive value 55.20%. With these findings, we could identify the imaging tests that best detected stenosis.**

Conclusion: **Tomography and Doppler showed good quality and efficacy in the diagnosis of renal artery stenosis, with Doppler having the advantage of not requiring the use of contrast medium for the assessment of a disease that is common in diabetics and is associated with renal dysfunction and severe left ventricular dysfunction. (Arq Bras Cardiol. 2013;101(5):423-433)**

Keywords: **Renal Artery Obstruction / diagnosis; Doppler, Echocardiography; Renal Artery Obstruction / radionuclide imaging; Magnetic Resonance Imaging; Hypertension, Renovascular.**

Introduction

Arterial Hypertension (AH) is a public health problem. Its relation to other diseases such as diabetes mellitus (DM), heart failure (HF), chronic kidney disease (CKD), and peripheral obstructive arterial disease (POAD) modifies the cardiovascular morbidity and mortality[1-3]. The growing incidence of atherosclerosis in the adult population, the presence of arterial obstruction leading to reduced renal blood flow and subsequent renovascular hypertension have aroused great interest for studies to be conducted in this field.

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The identification of a causal relation between arterial stenoses and AH has the additional advantage that revascularization procedures may be decisive for blood pressure control.

No study on the assessment of the sensitivity, specificity, and positive and negative predictive values of imaging tests for the diagnosis of renal artery stenosis in the same population is available in the Portuguese language. In a search conducted at the electronic address www.ncbi.nlm.nih.gov, the comparative analysis between diagnostic methods for renal artery stenosis (RAS) was found in few studies published recently[4,5].

Doppler, renal scintigraphy and computed tomography of the renal arteries were the imaging tests performed and compared with the reference standard, i.e, digital renal arteriography. The renin test and magnetic resonance angiography were also part of the study. However, due to the poor reproducibility of the renin test to predict RAS and because magnetic resonance angiography results were very similar to those of tomography, these two diagnostic methods were excluded[4-7].

Objective

To define the sensitivity, specificity, positive and negative predictive values of each of the noninvasive imaging tests.

To evaluate if there is a relation between risk factors for atherosclerotic disease and the presence of significant obstructions detected on invasive angiography of the renal arteries.

Methods

Prospective cohort study including 61 patients recruited between January 2008 and August 2011. Participants were duly registered and being followed up in our institution. The study was approved by the Institutional Research Ethics Committee, under number 3592.

All volunteers were informed about the nature of the study and gave written informed consent. Then, invasive and noninvasive diagnostic tests were performed to determine the presence or absence or RAS.

The flowchart containing the sequence of procedures performed was equally followed for all participants.

The first stage encompassed history taking, clinical examination and blood pressure measurement, according to the standardization of the VI Brazilian Guidelines on Arterial Hypertension[8]. Then, the medication used was recorded, and the patient received additional advice on how to correctly use the antihypertensive drugs. Patients using drugs that could interfere with the renin-angiotensin-aldosterone axis had these medications replaced by another class, without affecting blood pressure control, with the objective of maintaining their blood pressure levels equal to or lower than 140 x 90 mmHg.

Diabetic patients on metformin had the medication discontinued for at least 48 hours prior to any procedure using iodinated contrast medium. The medication was resumed 72 hours after the use of the iodinated contrast medium, due to the possibility of renal function impairment[9].

Only patients with AH and clinically suspected renovascular disease of atherosclerotic etiology who used antihypertensive medication at the moment of patient selection were included, regardless of age, gender, race, religion, socioeconomic condition, cardiovascular diseases or other comorbidities, provided that they met the inclusion criteria but not the exclusion criteria. We selected only cases presenting with at least two indicators of a medium or high probability as proposed by Pickering[10] (Table 1). Later, all patients underwent the tests selected for the present study.

Inclusion criteria

The inclusion criteria were: age between 18 and 80 years; clinical picture consistent with atherosclerosis; patients with AH (whether controlled or not); stages 2, 3 or resistant hypertension; onset of hypertension before 30 years of age or after 50 years of age; presence of abdominal or lumbar murmurs; evident atheromatous disease in coronary arteries, carotid arteries or peripheral vessels; smokers; pulse asymmetry; renal failure not related to other causes; acute pulmonary edema with no apparent cause; significant arterial hypotension during treatment with angiotensin converting enzyme inhibitors; refractory or malignant AH with progressive renal failure; elevation of serum creatinine with the use of angiotensin enzyme inhibitors; asymmetry of renal size or function; agreement to participate in the study; giving written informed consent.

Exclusion criteria

The exclusion criteria were: history of allergic reaction to iodinated contrast medium; women of childbearing age without a negative pregnancy test; inability or refusal to understand the study and give written informed consent; estimated calculation of glomerular filtration lower than 30 mL/min/m^2; patients with congestive heart failure (CHF); patients with coagulation disorders; patients with left ventricular dysfunction (ejection fraction < 40%); recent myocardial infarction (within the 6 months prior to the beginning of the study); acute coronary syndromes, recent stroke (within the 6 months prior to the beginning of the study).

Diagnostic tests

Laboratory tests

All patients were tested for the following laboratory tests: fasting blood glucose, uric acid, sodium and potassium, BUN and creatinine, complete blood count, thyroid stimulating hormone (TSH), and lipid profile. Creatinine clearance, which was important for the assessment of renal function impairment and for decision making in other stages of the study, was estimated using the Cockcroft Gault formula adjusted for body surface and corrected for gender[11].

Noninvasive imaging tests

Renal artery Doppler

A Toshiba high-resolution device with a convex multi-frequency transducer (3 to 5 MHZ) was used. Images were stored in VHS and included measurements for the detection of renal artery stenosis both direct and indirectly. The origin of both renal arteries was assessed from a cross-sectional view of the aorta, in B mode and with color flow, seeking to visualize the longest possible extent of the vessel, the presence of turbulence and flow abnormalities, observing the relationship between the systolic and diastolic velocity curves, and the calculation of the renal-aortic ratio (RAR). From this calculation, we were able to define whether the arteries were free from stenosis, and to verify the presence of cases with stenoses affecting more or less than 60% of the vessel diameter, according to criteria described in Table 2[12].

The imaging study of the renal arteries was complemented by the indirect analysis carried out with the patient in the left lateral position and right lateral position. From these recordings, the longitudinal diameter of the kidneys was compared. These images also permitted a better exploration of the distal portion of the renal arteries in which the intrarenal blood flow was evaluated using Doppler in the segmental or interlobar arteries, in three different segments (upper, mid- and lower); and the acquisition of velocity curves (systolic and diastolic) with the objective of analyzing the resistance

Table 1 - Clinical indicators of the probability of renovascular hypertension and investigation proposal

Probability	Características clínicas
Low (0.2%)	Borderline hypertension Non-complicated mild/moderate hypertension
Moderate (5-15%)	Severe or refractory hypertension Recent onset hypertension below 30 years or above 50 years Presence of abdominal or lumbar murmurs Radial or carotid pulse asymmetry Moderate hypertension, smokers, or atherosclerosis in other sites (coronary or carotid artery) Undefined renal function deficit Excessive pressure response to ACEI
Alta (25%)	Severe or refractory hypertension with progressive renal failureHipertensão acelerada ou maligna Accelerated or malignant hypertension Creatinine increase induced by ACEI* Asymmetric renal size or function

ACEI: angiotensin converting enzyme inhibitor.

index (RI), considering that normal values range from 0.56 and 0.7, and normal values for the flow acceleration time (AT) when shorter than 70 ms.

Tc-99m DTPA renal scintigraphy

Scintigraphic assessments were made using a Millennium VG gamma camera (GE Medical Systems, Milwaukee, USA).

Angiotensin inhibitors and/or angiotensin II-receptor blockers were discontinued for three days prior to the test.

For the baseline acquisition of the radioisotope renogram, the patients were placed in the supine position, so as to place the gamma-camera next to the kidneys and in direct relation to these organs. An intravenous access large enough to support a 7-Gauge or larger needle was established. After proper camera calibration, the radiotracer at a dose of 150 uCi/kg was injected in bolus until a maximum volume of 1 mL was reached. From this moment on, image recording was started.

After this initial acquisition, data started to be obtained using an angiotensin II converting enzyme inhibitor. In this phase, the administration of technetium-99-labeled diethylenetriaminepentaacetic acid 150 uCi/kg was repeated up to the maximum volume of 1 mL. Sixty minutes prior to this phase, the patients received a Captopril pill at a dose of 50 mg and had their blood pressure monitored. The gamma-camera remained in the same position as in the previous phase, and the same intravenous access and technique for radiotracer administration were used.

Table 2 - Criteria for the identification of the degree of stenosis

Degree of stenosis	SVP in main renal artery	RAR
Normal	< 180 cm/s	< 3,5
< 60%	≥ 180 cm/s	< 3,5
> 60%	≥ 180 cm/s	≥ 3,5
Occlusion	Absence of flow	Absence of sign

SVP: systolic velocity peak; RAR: renal aortic ratio.

When necessary, mapping was repeated after intravenous injection of furosemide 40 mg, 20 minutes after the Tc-99m DTPA injection.

Interpretation of the imaging test included the recording of the radiotracer transit time from the abdominal aorta to the kidneys, considering a normal value of up to 6 seconds. Another parameter analyzed was the tracer accumulation time in the kidneys, which reflects the glomerular filtration rate, whose normal value is usually between 3 and 5 minutes, followed by the excretion phase which in general lasts 20 to 30 minutes.

Computed tomographic angiography of the kidneys and renal arteries

The Aquilion® 64 multiple-detector tomographer (Toshiba Medical Systems, Ottawara, Japan) was used in this study.

Image acquisition of the arteries started by puncture of a peripheral vein large enough to permit the administration of the iodinated contrast medium at a rate of at least 3 mL/s. Thus, the acquisition of tomographic data was started by the record of a single localizer to identify the positioning of the segment to be studied. After the specific area of interest to be documented was defined, images were obtained using the injection of the contrast medium at a dose of 1.50 mL/kg of body weight at a rate of at least 3.50 mL/s. The programming included the use of 1-mm collimation, with a tube rotation time of 500 ms and table speed of 1.50 mm per tube rotation. During image recording, the patients were asked to perform a breath-hold, so as to limit the amount of artifacts resulting from the respiratory movements.

In order to obtain the volumetric representation of the morphology of the kidneys and renal arteries, the increment between anatomical sections, i.e., the distance from one image to the next was shorter than the thickness of the cross-sectional views obtained. After acquisition, data were transferred to a work station (Vitrea, Vital Images, California, USA), in which the post-processing was carried out, thus permitting the reconstruction of the patient's anatomy in different planes. Semi-objective measurement algorithms were used to measure

the reference diameters and minimum lumen diameter which, in turn, could allow the diagnosis of the presence of stenoses and, in positive cases, the estimate of their severity.

Invasive imaging tests

The gold-standard chosen in this study was the invasive assessment of the anatomy of the renal arteries using angiography. Since the vessels are more effectively assessed by contrasting the target arteries, an iodinated contrast medium was used. Because of this procedure, saline solution was administered before and after the test when renal dysfunction, as characterized by a creatinine clearance between 90 mL/min/1.73m^2 and 30 mL/min/1.73m^2, was present. Saline solution was administered at a dose of 10 mL/kg of body weight before and after image acquisition, at a rate that varied according to the patients' clinical status and ventricular function.

Digital renal arteriography

Renal arteriography was performed by the Section of Interventionist Radiology, using an Axiom Artis 2005 digital angiography equipment (Siemens, Germany), with flat detector for cardiovascular diagnosis. The procedure started by positioning the patient in the supine position in the digital hemodynamic laboratory; puncture of the femoral artery after local anesthesia with 2% lidocaine without vasoconstrictor was then performed. Next, a 5F valved introducer was advanced inside the right femoral artery; within which a 0.35 guide wire was introduced; a high-flow pigtail catheter was then advanced over the guide wire. It was used to opacify the abdominal aorta. Then, the renal arteries were selectively catheterized and the arterial, parenchymatous and venous phases were observed. The contrast material used was a water-soluble, ionic, low-osmolarity medium. Images were acquired using a digital subtraction filter and stored in a compact disc for further analysis.

After image acquisition, the introducer was removed and effective local compression was kept for a minimum period required.

Based on previous studies, the criterion used for the definition of a significant stenosis was an arterial lumen reduction by at least 60%, since there are data suggesting that these plaques are those which promote an average systolic gradient higher than 20 mmHg, thus being able to lead to renal tissue ischemia[13,14].

Statistical analysis

Data were described as absolute (n) and relative (%) frequencies for qualitative measures. Mean summary statistics, standard deviation (SD), median and 25th and 75th percentiles (Per 25 and Per 75) were used for quantitative measures.

The effect of the risk factors and other diagnostic tests on the results of the reference test (arteriography) was analyzed. The Pearson chi square test or Fisher's exact test was used to analyze the association between qualitative measures and the reference test. Comparison of quantitative measures between the response categories of arteriography was made using the Student's or Mann-Whitney t test.

Information regarding sensitivity and specificity, positive and negative predictive values are presented.

The agreement level between two diagnostic methods and digital arteriography was analyzed using the Kappa method.

Positive values of the diagnostic tests should occur when the stenosis diameter was > 60%.

The significance level of the tests was set at 5%.

The analyses were carried out using the Statistical Package for the Social Sciences (SPSS) 19.0 (SPSS Inc., Chicago IL, 2004) software program.

Results

Between January 2008 and August 2011, 63 individuals were recruited. Of these, 61 underwent all tests, except for one patient who did not undergo DTPA radioisotope renogram. Thirty three patients were women; the mean age was 65.43 (± 8.7) years, the mean weight was 71.45 (± 11.83) kg and the mean height was 1.59 (± 0.97) m. Approximately half of the study population had DM and several patients had clinical manifestations of atherosclerosis; however, the number of participants with smoking habit and POAD was not significant. Patient demographics and their clinical characteristics are shown in Table 3.

Lipid profile abnormalities were found in more than one third of cases. Renal function, as assessed using the adjusted Cockcroft Gault formula, showed renal dysfunction in most of the cases.

The noninvasive imaging tests revealed abnormalities suggestive of the presence of significant stenoses in renal arteries in more than two thirds of the study population. These results were similar to those found in invasive arteriography.

Sensitivity, specificity, and predictive value of the noninvasive imaging tests

The relation between the results obtained with invasive and noninvasive imaging tests was analyzed by comparing the individual results of each study patient. The initial analysis showed a significant correlation of the results of Doppler and tomography with invasive angiography (Table 4). The results of the scintigraphic study were not significantly associated with those of angiography.

Sensitivity, specificity, positive and negative predictive values of the noninvasive imaging tests, as well as the Kappa value were also defined. Again, arteriography was used as the reference test. Results of the analyses per patient and per vessel are shown in Tables 5 and 6.

Association between risk factors and renal arteriography findings

As proposed, the association between the presence of stenoses above 60% and the different risk factors of the whole population was analyzed. Results are shown in Table 7. The presence of abnormal triglyceride levels, renal dysfunction, high creatinine levels, and decreased glomerular filtration rate were predictive of the existence of significant obstructive plaques in at least one of the renal arteries.

Consistency of noninvasive imaging test results was verified by analyzing the results of the interobserver interpretation, i.e., other experienced examiners were asked to quantify the percentage of stenosis in the renal arteries 12 to 18 months after the initial analysis. The results included in the analysis, in turn, were decided by consensus between the two operators, in case of disagreement regarding the findings.

The results presented in Table 8 show a high level of agreement between tests, except for scintigraphy, which showed intermediate results, albeit significant.

Discussion

Arteriography remains as the gold-standard test for the diagnosis of renal artery stenoses; however, it is still related to the occurrence of complications, especially in cases of higher risk and greater number of comorbidities[15].

The findings of this study demonstrate that the association of noninvasive imaging tests may provide important information on the presence of significant renal artery stenosis. Abnormalities found in Doppler and tomography are frequently accompanied by significant reductions in the arterial lumen; however, some peculiarities of this study deserve special consideration.

The study population reproduced many of the aspects associated with the presence of obstructive atheromatous plaques in the renal arteries described in the literature.

Age above 60 years and white ethnicity – characteristics found in our study patients, are usually the major predictors of atherosclerotic disease[16].

One of the risk factors commonly associated with renovascular disease of atherosclerotic origin is cigarette smoking, especially in the presence of POAD. The present study showed a situation different from that seen in the literature, because the proportion of smokers or patients with POAD was not significant, of 13.1% and 21.3%, respectively.

Given that this is a population at a high cardiovascular risk, a higher incidence of coronary artery disease and carotid artery disease was expected. However, even with the use of different methods to identify these diseases, the incidence found was low, of 39.3% and 26.2%, respectively.

Patients were recruited from the Dante Pazzanese Institute of Cardiology, where anti-tobacco campaigns, frequent use of lipid-lowering drugs and proper dietary guidance are in place, and this may have been the reason for the lower incidence found for those diseases.

A meta-analysis on the prevalence of renovascular disease in several risk groups found DM in 20% of their study population[17]. The prevalence found in our study is 2.5 times higher (50.8%).

Although hyperlipidemia is frequently identified in populations with atherosclerotic disease, to date no study has confirmed that this association is predictive of RAS[18]. In this study, high total cholesterol and LDL-cholesterol levels were not found; the levels verified were strictly within normal limits. This lipid profile may provide this population with a better clinical perspective, even considering the fact that 78.7% of participants showed HDL-cholesterol levels lower than the minimum gender-required levels. Also, the triglyceride profile in the study population also showed values lower than those considered atherogenic. This may also be explained by the fact that all patients' plasma lipid levels were under strict control[19].

Diagnosis of RAS and the diagnostic tests

Doppler, CT angiography and magnetic resonance imaging have been exceptionally accepted as tests for the diagnosis of diseases of the thoracic and abdominal aorta, as well as for those of the infrainguinal vessels. However, this is not valid for the study of the renal arteries.

The analysis of the association between noninvasive tests and digital arteriography shows a clear correlation of Doppler and CT angiography with digital arteriography, both in the analysis per patient and per vessels, all with p values ≤ 0.05. This was not observed for scintigraphy.

Analysis of sensitivity, specificity, positive and negative predictive values of the noninvasive diagnostic tests

The role of each imaging method used in individuals with suspected renal artery stenosis was compared. We then proposed a better population selection and the identification of the best tests to guide the diagnosis.

Doppler

Measurements found for the assessment of sensitivity and specificity of Doppler of the renal arteries in probable RAS showed values of 82.90% and 70%, respectively, which correspond to a positive predictive value of 85% and a negative predictive value of 66.70%. The Kappa value of 0.523 showed a moderate level of agreement with the reference standard, with $p < 0.001$.

These values make Doppler an interesting diagnostic option for the investigation of atherosclerotic renovascular disease, because the test was able to identify stenosis in a population with RAS, to rule out the disease in patients not having it, and to identify it among those with a positive test. This was achieved with reasonable safety, and the values found in the present study corroborate those reported in the literature.

We may conclude that sensitivity, specificity and the positive and negative predictive values make this test an important diagnostic tool for the investigation of atherosclerotic renovascular disease, despite the many limitations regarding the applicability of the method described in the literature[20,21].

Renal scintigraphy

With low sensitivity and positive predictive values (12.50% and 45.50%, respectively), and reasonable specificity, but a low negative predictive value (70% and 28.60%, respectively), the performance of scintigraphy in this population was not as good as that of Doppler, and this was reflected in the finding of a Kappa value of (-) 0.128. Values lower than zero identify total disagreement between the findings from scintigraphy and digital renal arteriography

We should also point out that low significance values were found for the other analyses carried out, both for patients and for arteries.

Table 3 - Descriptive statistics of the population characteristics, categorical variables

Population		n	%
Gender	F	33	54.1
	M	28	45.9
Ethnicity	Black	14	23
	White	47	77
Age > 60 years	No	17	27.9
	Yes	44	72.1
Cigarette smoking	No	53	86.9
	Yes	8	13.1
BMI range	Normal	17	27.9
	Overweight	26	42.6
	Obesity 1	9	14.8
	Obesity 2	9	14.8
DM2	No	30	49.2
	Yes	31	50.8
TC > 200 mg/dL	No	41	67.2
	Yes	20	32.8
HDL risk (M < 40/F < 50)	No	13	21.3
	Yes	48	78.7
LDL	LDL < 100 mg/dL	30	49.2
	100 ≤ LDL ≤ 130 mg/dL	18	29.5
	LDL > 130 mg/dL	13	21.3
TG > 150 mg/dL	No	33	54.1
	Yes	28	45.9
AC risk (M > 102/F > 88)	No	24	39.3
	Yes	37	60.7
POAD	No	48	78.7
	Yes	13	21.3
CAD	No	37	60.7
	Yes	24	39.3
Carotid artery disease	No	45	73.8
	Yes	16	26.2
Proteinuria	No	50	82
	Yes	11	18
Renal dysfunction	No	9	14.8
	Yes	52	85.2
	Mean (SD)	**Median (Per 25; Per 75)**	
Age (years)	65.43 (8.7)	66.0 (59.5;72.5)	
Weight (kg)	71.45 (11.83)	70.4 (64.0;77.0)	
Height (m)	1.59 (0.97)	1.59 (1.50;1.68)	
Body surface (m^2)	1.73 (0.16)	1.75 (1.61;1.83)	
Creatinine (mg/dL)	1.26 (0.47)	1.20 (0.90;1.54)	
Adjusted Cockcroft Gault (mL/min/1,73 m^2)	61.0 (24.6)	52.8 (41.1;74.4)	

F: female; M: male; BMI: body mass index; DM2: type-2 diabetes mellitus; TC: total cholesterol; HDL: high density lipoproteins; LDL: low density lipoproteins; TG: triglycerides; AC: abdominal circumference; POAD: peripheral obstructive arterial disease; CAD: coronary artery disease; SD: standard deviation; Per 25: 25th percentile; Per 75: 75th percentile.

Table 4 - Association between the diagnostic tests and digital arteriography

		Right arteriography				Left arteriography				Arteriography			
		Negative (n = 39)	Positive (n = 22)	Total (n =61)	P value	Negative (n = 32)	Positive (n = 29)	Total (n = 61)	P value	Negative (n = 20)	Positive (n = 41)	Total (n = 61)	P value
CT angiography													
Negative	n	36	12	48	**0.001**	30	7	37	**< 0.001**	16	13	29	**<0.001**
	%	92.31	54.55	78.69		93.75	24.14	60.66		80.00	31.70	47.50	
Positive	n	3	10	13		2	22	24		4	28	32	
	%	7.69	45.45	21.31		6.25	75.86	39.34		20.00	68.29	52.46	
Scintigraphy													
Negative	n	32	18	50	1.000F	25	26	51	0.474F	14	35	49	0.155F
	%	82.05	85.71	83.33		80.65	89.6	85.00		70.00	87.50	81.67	
Positive	n	7	3	10		6	3	9		6	5	11	
	%	17.95	14.29	16.67		19.35	10.34	15.00		30.00	12.50	18.33	
Doppler													
Negative	n	30	8	38	**0.002**	29	7	36	**< 0.001**	14	7	21	**i**
	%	76.92	36.36	62.30		90.63	24.14	59.02		70.00	17.10	34.40	
Positive	n	9	14	23		3	22	25		6	34	40	
	%	23.08	63.64	37.70		9.38	75.86	40.98		30.00	82.90	65.6	

Pearson chi square test.

Table 5 - Sensitivity, positive predictive value (PPV) and Kappa measurement for the diagnostic tests

		Sensitivity (%)	PPV (%)	Agreement (Kappa)	
				Medida Kappa	p value
Patients (n = 61)					
Doppler (n = 61)	Left kidney	75.90	88.00	0.669	< 0.001
	Right kidney	63.60	60.90	0.402	0.002
	General	82.90	85.00	0.523	< 0.001
Scintigraphy (n = 60)	Left kidney	10.30	33.30	-0.092	0.329
	Right kidney	14.30	30.00	-0.420	0.717
	General	12.50	45.50	-0.128	0.099
CT angiography (n = 61)	Left kidney	75.90	91.70	0.702	< 0.001
	Right kidney	45.50	76.90	0.415	0.001
	General	68.30	87.50	0.433	< 0.001
Arteries (n = 122)					
Doppler (n = 122)		70.60	75.00	0.541	< 0.001
Scintigraphy (n = 120)		12.00	31.60	-0.072	0.453
CT angiography (n = 122)		62.70	86.50	0.579	< 0.001

This diagnostic method is based on the radiotracer arrival, accumulation and clearance curves, thus directly depending on the degree of the renal structure integrity to identify stenosis of a vessel. Therefore, these results do not allow us to consider scintigraphy of the renal arteries as a test indicated for the diagnosis of RAS in patients with impaired renal function. Thus, we can conclude that scintigraphy is not recommended in populations with renal dysfunction.

CT angiography

With superior results, although very close to those found using Doppler, CT angiography proved to be a very useful test for the identification of individuals with RAS. The sensitivity, specificity, positive and negative predictive values found (68.30%, 80.00%, 87.50% and 55.20%, respectively) showed that this noninvasive imaging test is a very useful diagnostic

Table 6 - Specificity, negative predictive value (NPV) and Kappa measure for the diagnostic tests

Patients (n = 61)		Specificity (%)	NPV (%)	Agreement (Kappa)	
				Kappa measure	p value
CT angiography (n = 61)	Left kidney	93.80	81.10	0.702	< 0.001
	Right kidney	92.30	75.00	0.415	0.001
	General	80.00	55.20	0.433	< 0.001
Scintigraphy (n = 60)	Left kidney	80.60	49.00	-0.092	0.329
	Right kidney	82.10	64.00	-0.420	0.717
	General	70.00	28.60	-0.128	0.099
Doppler (n = 61)	Left kidney	90.60	80.60	0.669	< 0.001
	Right kidney	76.90	78.90	0.402	0.002
	General	70.00	66.70	0.523	< 0.001
Artéries (n = 122)					
CT angiography (n = 122)		93.00	77.60	0.579	< 0.0001
Scintigraphy (n = 120)		81.40	56.40	-0.072	0.453
Doppler (n = 122)		83.10	83.10	0.541	< 0.0001

tool. Kappa values showing moderate agreement (0.433) and a significance level of $p < 0.001$ confirm this statement.

Several studies have used this diagnostic method to investigate RAS[22,23].

For CT angiography, limitations regarding the use of a contrast medium may be important. In younger populations, radiation exposure should be considered.

Analysis of the association between risk factors and renal arteriography

The relationship between lesions considered greater than a 60% reduction in vessel lumen, as quantified by visual analysis of the angiogram, was analyzed in order to identify the presence of an association between risk factors and digital arteriography.

This analysis permitted the identification of two variables – renal dysfunction and plasma triglyceride levels, among the risk factors allocated in this study, as being able to establish a causal relationship between an obstructive plaque in the renal artery and the risk factors previously mentioned.

Even with the possibility of being represented by any of the variables that identify renal dysfunction, the body surface-adjusted creatinine clearance corrected by gender was the variable chosen to demonstrate the relationship between renal dysfunction and the presence of stenosis, because there is an important correlation between its values and cardiovascular disease mortality. Thus, identifying renal artery stenosis is an important condition to minimize the progression of the cardiovascular disease itself.

The findings of the present study identified a median creatinine clearance of 52.8 (41.1; 74.4) mL/min/m^2. These values correspond to glomerular filtration rates consistent with stage-3 renal dysfunction, which precisely characterize individuals at a higher risk for cardiovascular events[24].

In this study, 85.2% of the participants had renal dysfunction. In the statistical analysis of the quantified measures, this risk factor was predictive of the presence of stenosis > 60% in at least one of the renal arteries, with $p \leq 0.002$.

Plasma triglyceride levels were another risk factor that showed an association with renal artery stenosis. However, we observed an inverse relation to the one usually found. In this population, we found a lower chance of RAS in patients with plasma triglyceride levels > 150 mg/dL. Another form of interpreting the results would be to imagine that higher triglyceride levels could bring some protective effective in the development of the obstructive renal plaque. In our study population, these findings reached a clinical significance level, with $p < 0.037$, and should thus be interpreted.

However, it is a fact that the literature does not identify the possibility of the development of atherosclerotic disease per se in populations like this. In the presence of lower triglyceride levels, other comorbidities could be present to justify the development of atherosclerotic disease.

Increased plasma triglyceride levels are usually associated with the presence of risk factors such as obesity, metabolic syndrome, pro-thrombotic states, pro-inflammatory states and type-2 DM, all contributing for an increased risk of cardiovascular diseases. The NCEP ATPIII[25] identified that levels < 150 mg/dL and between this value and 200 mg/dL had a smaller participation in the assessment of the cardiovascular risk alone. However, values > 200 mg/dL (hypertriglyceridemia) are already considered as an independent risk factor for cardiovascular diseases.

We should remember that this population comprised individuals aware of their morbid condition and who were already taking medications that aimed not only to control their blood pressure, but also all the risk factors involved in atherosclerotic diseases.

From these findings, we can state that the presence of atherosclerotic disease in other sites, the metabolic syndrome components, and other risk factors that are present in the population, other than renal dysfunction and triglyceride levels, did not identify RAS.

Table 7 - Association between risk factors and digital arteriography

	Arteriography		Total	p value
	Negative (n = 20)	Positive (n = 41)	n = (61)	
Male gender n (%)	7 (35)	21 (51.22)	28 (45.9)	0.233
White ethnicity n (%)	17 (85)	30 (73.17)	47 (77.05)	0.302
Age > 60 n (%)	13 (65)	31 (75.61)	44 (72.13)	0.386
Cigarette smoking n (%)	3 (15)	5 (12.2)	8 (13.11)	0.761
Normal BMI n (%)	5 (25)	12 (29.27)	17 (27.87)	0.659
IMC sobrepeso n (%)	7 (35)	19 (46.34)	26 (42.62)	
BMI obesity 1 n (%)	4 (20)	5 (12.2)	9 (14.75)	
BMI obesity 2 n (%)	4 (20)	5 (12.2)	9 (14.75)	
DM2 n (%)	9 (45)	22 (53.66)	31 (50.82)	0.525
TC > 200 mg/dL n (%)	7 (35)	13 (31.71)	20 (32.79)	0.797
HDL risco (M < 40/F < 50) n (%)	15 (75)	33 (80.49)	48 (78.69)	0.623
LDL < 100 mg/dL n (%)	10 (50)	20 (48.78)	30 (49.18)	0.373
100 ≤ LDL ≤130 mg/dL n (%)	4 (20)	14 (34.15)	18 (29.51)	
LDL > 130 mg/dL n (%)	6 (30)	7 (17.07)	13 (21.31)	
TG > 150 mg/dL n (%)	13 (65)	15 (36.59)	28 (45.9)	0.037
AC risk (M > 102/F > 88) n (%)	14 (70)	23 (56.1)	37 (60.66)	0.297
POAD n (%)	4 (20)	9 (21.95)	13 (21.31)	0.861
CAD n (%)	8 (40)	16 (39.02)	24 (39.34)	0.942
Carotid artery disease n (%)	3 (15)	13 (31.71)	16 (26.23)	0.164
Proteinuria n (%)	4 (20)	7 (17.07)	11 (18.03)	0.780
Renal dysfunction n (%)	13 (65)	39 (95.12)	52 (85.25)	0.002
Age (years) mean (DP)	62.95 (9.89)	66.63 (7.92)	65.27 (8.61)	0.122t
Median (Per 25; Per75)	63.5 (53;70.75)	66 (60.5;73)	65 (59;72)	
Height (m) Mean (SD)	1.59 (0.1)	1.59 (0.1)	1.59 (0.1)	0.824M-W
Median (Per 25; Per75)	1.62 (1.49;1.65)	1.59 (1.5;1.69)	1.59 (1.5;1.68)	
Weight (kg) Meana (SD)	71.97 (13.4)	71.2 (11.15)	71.18 (11.73)	0.945M-W
Median (Per 25; Per75)	70 (65.43;82.25)	71 (64;77)	70 (64;77)	
Body surface (m^2) mean (SD)	1.74 (0.18)	1.73 (0.15)	1.73 (0.16)	0.896t
Median (Per 25; Per75)	1.72 (1.61;1.81)	1.76 (1.61;1.83)	1.73 (1.61;1.82)	
Creatinine mg/dL mean (SD)	0.96 (0.32)	1.41 (0.47)	1.27 (0.47)	< 0.001M-W
Median (Per 25; Per75)	0.92 (0.7;1.24)	1.3 (1.05;1.8)	1.25 (0.9;1.58)	
CG mean (SD)	88.74 (34.21)	56.88 (20.81)	66.63 (29.56)	0.001t
Median (Per 25; Per75)	82.78 (59.47;106.73)	55.76 (42.91;66.85)	58.67 (46;82.41)	
Adjusted CG mean (SD)	79.09 (28.51)	52.05 (17.08)	60.3 (24.65)	0.001t
Median (Per 25; Per75)	72.27 (56.12;104.5)	49.39 (40.04;62.69)	53.98 (43.03;70.68)	
CG mean body surface (SD)	78.99 (27.25)	52.23 (17.7)	60.44 (24.39)	< 0.001t
Median (Per 25; Per75)	77.05 (52.76;101.98)	47.97 (38.35;63.53)	52.75 (41;72.29)	

Pearson chi square test; t: Student t test; M-W: Mann-Whitney test. BMI: body mass index; DM2: type-2 diabetes mellitus; TC: total cholesterol; HDL: high density lipoproteins; LDL: low density lipoproteins; TG: triglycerides; AC: abdominal circumference; POAD: peripheral obstructive arterial disease; CAD: coronary artery disease; SD: standard deviation; Per 25: 25th percentile; Per 75: 75th percentile; CG: Cockcroft Gault.

Table 8 - Agreement between observers of the different noninvasive imaging tests

	Kappa	Valor de p
Arteriography	0.8925	< 0.001
CT angiography	0.9362	< 0.001
Scintigraphy	0.5140	< 0.001
Doppler	0.9647	< 0.001

Conclusions

The findings of the present study demonstrated that it is possible to identify the presence of renovascular disease using an association of noninvasive imaging tests in most of the cases.

Sensitivity, specificity, and the positive and negative predictive values of Doppler and tomography are satisfactory, unlike what was observed with renal scintigraphy. Renal dysfunction and low triglyceride levels were the only risk factors associated with the presence of stenosis, as detected by the visual analysis of arteriography.

Finally, considering the investigation process and all the methodology and analyses carried out, Doppler and CT angiography showed a satisfactory correlation with the analysis of the renal artery lumen as seen in the angiogram, unlike in scintigraphy. However, we should bear in mind that these results apply to patients with characteristics similar to those of this study population, and that Doppler ultrasonography is operator-dependent. Although tomography is under less influence of the physician who conducts the test, it is less frequently available in Brazil.

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Writing of the manuscript: Borelli FAO, Pinto IMF, Amodeo C; Acquisition of data: Borelli FAO, Paiva RC, Lopes HB; Statistical analysis and Critical revision of the manuscript for intellectual content: Borelli FAO, Pinto IMF; Examinations of nuclear medicine: Smanio PEP; Realization of Doppler renal arteries: Petisco ACG; Performance of all renal arteriography: Kambara AM, Moreira SM; Infrastructure inpatient and outpatient: Sousa AGMR.

Potential Conflict of Interest

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

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