

## Research of multiarterial atherosclerotic disease in hypertensive patients with renal artery stenosis

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### ABSTRACT

**Introduction:** The detection of the renal artery stenosis in hypertensive patients can be a signal of systemic arterial atherosclerosis. **Aims:** To identify and characterize clinical-epidemiologically the hypertensive patients with renal artery stenosis, evaluating factors of cardiovascular risk and presence of symptomatic multiarterial atherosclerotic. **Method:** Were selected the hypertensive patients who were assisted at the Nephrological Clinic of Universidade Federal do Triângulo Mineiro (UFTM) between 2000-2010, with diagnosis of renal artery stenosis of atherosclerotic etiology. Epidemiological data were evaluated (gender, age, ethnicity), factors of cardiovascular risk (diabetes, hypercholesterolemia, hypertriglyceridemia, tabagism, metabolic syndrome), information on hypertension (time of diagnosis, family report, number of used medicines), previous cardiovascular events (acute myocardial infarction, ischemic stroke, peripheral arterial disease). Blood pressure levels, global cardiovascular risk and Score Framingham were stratified. **Results:** Casuistry of 30 patients, feminine majority (73.3%), average of 66 year-old age, 86.67% white, medium time of hypertension of 19.94 years, 89.92 without family report, 13.8 with diabetes, 65.51% smoking, 17.25% hypertriglyceridemia, 62.06% with hypercholesterolemia and 66.7% with metabolic syndrome. Average number of medicines in use: 3.26. Dominant right-sided renal artery stenosis separately (46.7%) and in proximal third (56.7%). High creatinine levels in 40% of the patients. As for the hypertension phase, majority phase 2 (47%) and 73.3% with high global cardiovascular risk. Average Framingham Score of 13%. 66.7% presented atherosclerotic disease in another place, being infarction the

main one (53.3%). **Conclusion:** The most common correlation was with acute myocardial infarction, what implicates in the search of the coronary compromising to the diagnosis of renal artery stenosis in hypertensive patients to try avoid future damages to the patient.

**Keywords:** atherosclerosis, cardiovascular diseases, hypertension.

### INTRODUCTION

Systemic hypertension (SH) is a highly prevalent chronic disease, and its complications are of great impact to morbidity and mortality in the Brazilian and world populations.<sup>1</sup>

According to its etiology, SH can be classified in 2 subtypes: (1) primary/essential, which represents approximately 95% of SH cases and does not have a defined etiology, with an important genetic and environmental component; or (2) secondary, which corresponds to approximately 5% of cases and presents a defined etiology, given that some of these SH patients can be cured by treating the primary disease.<sup>1,2</sup>

Among the causes of secondary SH, parenchymal renal disease is the most frequent, followed by renovascular hypertension (RVHT), which is the most potentially curable cause of SH.<sup>2</sup> The 2 main causes of renal artery stenosis that lead to RVHT are atherosclerosis, which is responsible for 90% of cases, and fibromuscular dysplasia, corresponding to less than 10% of cases.<sup>3,4</sup>

Atherosclerotic disease has many causes and can affect any portion of the arterial bed; however, macrovascular

impairment occurs most frequently in the coronary, renal, carotid, and iliac-femoral arteries.<sup>5,6</sup> Risk factors for its development, such as hypertension, advanced age, diabetes mellitus, and dyslipidemia, are the same for these various sites, and the presence of atherosclerosis in several sites is not an uncommon finding.<sup>4,6</sup> According to some studies, the link between RVHT of atherosclerotic origin and multiartery atherosclerotic disease is common; however, only 1 concurrent arterial bed has been assessed in each study.<sup>4-8</sup>

Based on these data, the objectives of the present research were as follows: (1) identify and characterize, clinically and epidemiologically, hypertensive patients who had renal artery stenosis of atherosclerotic origin and were treated at the outpatient nephrology clinic of the Clinic Hospital of the Federal University of the Triângulo Mineiro; (2) stratify patients in relation to the stage of hypertension, risk factors for cardiovascular disease, individual global cardiovascular risk, Framingham score, and presence of metabolic syndrome; and (3) verify the presence of atherosclerotic cardiovascular events in this population, demonstrating the concomitance of renal artery stenosis of atherosclerotic origin and multiartery atherosclerotic disease in potentially affected areas (coronary, carotid, and peripheral artery circulation).

## METHODS

### PATIENT SELECTION

This study was a cross-sectional descriptive study. Patients were selected by analyzing the database of the patients treated at the outpatient clinic of Nephrology at the Federal University of the Triângulo Mineiro, between 2000 and 2010. These patients had been diagnosed with hypertension and renal artery stenosis of atherosclerotic etiology.

### CLINICAL AND EPIDEMIOLOGICAL CHARACTERIZATION

The assessments were conducted based on the following parameters: epidemiological data (gender, age, and ethnicity), information regarding hypertension (diagnosis time, family history, and the number of medicines used), laboratory results (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglyceride, and creatinine levels), and risk factors for cardiovascular

disease according to the VI Brazilian Guidelines of Hypertension<sup>9</sup> (age > 55 years for men and > 65 years for women, smoking, dyslipidemia: triglyceride level  $\geq 150$  mg/dL, LDL cholesterol level > 100 mg/dL, HDL level < 40 mg/dL, diabetes mellitus, premature family history of cardiovascular disease: < 55 years for men and < 65 years for women).

### DIAGNOSIS OF HYPERTENSION WITH RENAL ARTERY STENOSIS AND ASSESSMENT OF RENAL FUNCTION

The diagnosis of hypertension with renal artery stenosis was considered by observing the presence of hypertension characterized as systolic blood pressure (SBP)  $\geq 140$  mmHg or diastolic blood pressure (DBP)  $\geq 90$  mmHg,<sup>9</sup> linked to luminal stenosis in > 70% of the renal artery. This analysis was conducted at our center by using color Doppler ultrasound or arteriography, confirming atherosclerotic etiology on the basis of the characteristics of stenosis.<sup>10</sup>

Renal function was assessed by measuring serum creatinine levels, and values > 1.3 mg/dL for males and > 1.2 mg/dL for females were considered abnormal. After obtaining data for the patients' weight (kg), gender, age (years), and serum creatinine levels (mg/dL), the estimated glomerular filtration rate (mL/min) was calculated by the Cockcroft-Gault formula<sup>11</sup>. The patients were then stratified with regard to the degree of chronic renal insufficiency, according to their glomerular filtration rates: 0, > 90 (risk groups for chronic renal disease, but without renal lesion); 1, >90 (renal lesion with normal renal function); 2, 60-89 (mild renal insufficiency); 3, 30-59 (moderate renal insufficiency); 4, 15-29 (severe renal insufficiency); and 5, < 15 (terminal or renal insufficiency requiring dialysis).<sup>12</sup>

### PRESSURE LEVEL STRATIFICATION, GLOBAL CARDIOVASCULAR RISK, ASSESSMENT OF THE CRITERIA FOR METABOLIC SYNDROME, AND FRAMINGHAM SCORE

After obtaining the casual SBP and DBP measurements at the clinic, the patients were stratified according to BP levels into stage I (SBP, 140-159 mmHg and/or DBP, 90-99 mmHg), stage II (SBP, 160-179 mmHg and/or DBP, 100-109 mmHg), or stage III (SBP  $\geq 180$  mmHg or DBP  $\geq 110$  mmHg), according to the VI Brazilian Guidelines of Hypertension.<sup>9</sup> After obtaining the BP stratification by stage and the analysis of the cardiovascular disease risk factors,

the overall cardiovascular risk of the patients was also stratified in accordance with the aforementioned guidelines.

Metabolic syndrome was diagnosed in accordance with the recommendations of the I Brazilian Guideline for the Diagnosis and Treatment of Metabolic Syndrome,<sup>13</sup> corresponding to the combination of 3 of the following factors: abdominal obesity confirmed by waist circumference > 102 cm for men and > 88 cm for women, serum triglyceride level  $\geq$  150 mg/dL, HDL cholesterol level < 40 mg/dL for men and < 50 mg/dL for women, SBP  $\geq$  130 mmHg or DBP  $\geq$  85 mmHg, and fasting blood glucose level  $\geq$  110 mg/dL.

The Framingham score calculation<sup>14</sup> was applied to subjects who did not show prior history of coronary disease. The patients were assessed according to the following variables: gender, age, total cholesterol and HDL cholesterol levels, BP value, presence of diabetes, and smoking status. Each of these items received a specific score. The total number of points obtained was transformed into risk percentages for the occurrence of a severe cardiovascular event in the next 10 years by using estimates. Participants were then stratified into 3 categories according to the level of risk mentioned above: low risk (< 10%), intermediate risk (between 10% and 20%), and high risk (> 20%).

#### MULTIARTERY ATHEROSCLEROTIC DISEASE ANALYSIS

Multiartery atherosclerotic disease was diagnosed by analyzing patient records, which showed their clinical history; this analysis helped identify previous and current symptomatic cardiovascular diseases (acute myocardial infarction [AMI], ischemic encephalic vascular accident [iEVA], and peripheral artery disease [PAD]).

#### DATA ANALYSIS

For the statistical analysis, an electronic spreadsheet that contained the collected information was created. The data were analyzed and the results have been shown descriptively as percentage values.

#### ETHICAL ASPECTS

This research was approved by the Research Ethics Committee of the Federal University of the Triângulo Mineiro under protocol number 1594.

## RESULTS

At the Outpatient Nephrology Clinic of the Federal University of the Triângulo Mineiro, 33 patients underwent follow-up and had a diagnosis of hypertension with renal artery stenosis. Among these patients, 30 (90.9%) cases of hypertension were of atherosclerotic etiology, 2 (6%) were due to muscular fibrodysplasia, and 1 (3.1%) was due to polyarteritis nodosa.

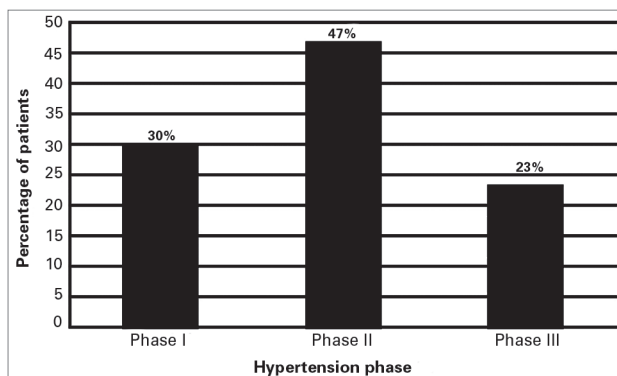
The patient gender distribution was as follows: women, 73.3%; and men, 26.7%. The average patient age was 66.06 years ( $\pm$  12.25 years); 86.67% of the patients were white and 13.33% were non-white. The average diagnosis time for hypertension was 19.94 years ( $\pm$  5.32 years), and 89.28% of patients did not have a family history of SH. Most patients did not have diabetes mellitus (86.20%), 65.51% were smokers, 17.25% had hypertriglyceridemia, and 62.06% had hypercholesterolemia. The average number of medicines used was 3.26 ( $\pm$  1.2).

Approximately 46.7% of the patients presented with renal artery stenosis only in the right renal artery, 20% had lesions only in the left renal artery, and 33.3% presented with bilateral lesions. The renal artery stenosis was located in the proximal third in 56.7% of the patients, and 43.3% had stenosis in the ostium. Approximately 40% of the patients showed high levels of serum creatinine, and 16.67% of the patients already showed chronic renal insufficiency under conservative treatment.

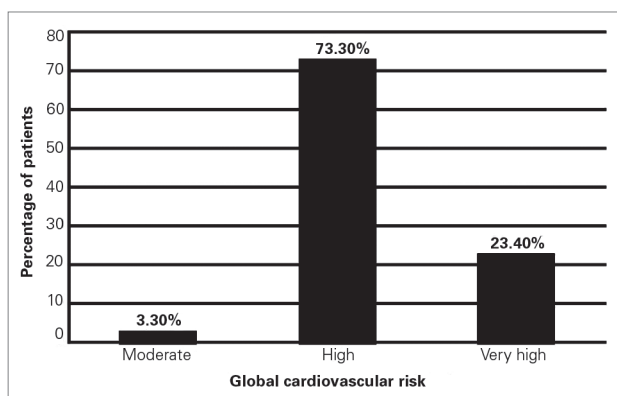
The distribution of patients with regard to the degree of arterial hypertension has been shown in Figure 1, and the distribution with regard to individual overall cardiovascular risk is shown in Figure 2. The Framingham Score of patients who did not have symptoms of coronary artery disease and who had never experienced a previous episode of AMI was 13% ( $\pm$  2%), that is, a 13% chance of developing coronary artery disease and infarction in 10 years, indicating medium risk. Approximately 66.67% of the patients met the criteria for metabolic syndrome.

By studying symptomatic atherosclerotic arterial diseases in coexistence with hypertension and renal artery stenosis, we found that these diseases were present in 66% of the patients. AMI was the most common condition (53.3% of the cases), followed by iEVA (30% of the cases) and PAD (16.67% of

**Figure 1.** Patient stratification according to blood pressure levels (VI Brazilian Guidelines of Hypertension).



**Figure 2.** Patient stratification according to the overall cardiovascular risk (VI Brazilian Guidelines of Hypertension).



**TABLE 1** CONCOMITANCE (IN PERCENTAGES) BETWEEN THE TYPES OF MULTIARTERY ATHEROSCLEROTIC DISEASE MANIFESTED IN HYPERTENSIVE PATIENTS WITH RENAL ARTERY STENOSIS OF ATHEROSCLEROTIC ORIGIN

AMI	53.3%
iEVA	30%
PAD	16.7%
AMI + iEVA	30%
AMI + iEVA + PAD	6.67%

AMI: acute myocardial infarction; iEVA: ischemic encephalic vascular accident; PAD: peripheral artery disease.

the cases). There was coexistence of AMI and EVA in 30% of the cases, and AMI, iEVA, and PAD in 6.67% of the cases (Table 1).

## DISCUSSION

Hypertension caused by renal artery stenosis results in an increase of BP due to renal ischemia caused by partial or total obstruction of 1 or both renal arteries.<sup>15,16</sup> Chronic ischemia may result in renal function disturbances, in addition to lack of BP

control, and may lead to salt and water retention disorders as well as renal endocrine function disorders.<sup>6</sup> It is critical to differentiate renovascular hypertension from renovascular disease, in which stenosis of the renal artery is also present. However, these lesions do not cause hypertension; therefore, if treated, it will not benefit the patient.<sup>16</sup>

In contrast to the findings reported in the literature in which males are most affected by hypertension with renal artery stenosis of atherosclerotic origin, representing up to 2/3 of cases,<sup>15</sup> in our study there was a higher prevalence in females. This finding could be explained by the fact that the patients in our study were predominantly elderly, and this stage of life is marked by an increase in cardiovascular risk in women due to the effects of decreased estrogen.<sup>17</sup> Moreover, women tend to seek medical services more frequently compared to men.<sup>18</sup>

According to the literature, hypertension with renal artery stenosis of atherosclerotic etiology is more common in elderly patients,<sup>5,6,16</sup> which was also observed in our sample, as the average age of the patients was 66.06 years. With an increase in the population's life expectancy, this disease tends to be ever more prevalent.<sup>5</sup> A plausible explanation for the increase in hypertension with renal artery stenosis of atherosclerotic origin due to aging is that senility is associated an increase in the prevalence of comorbidities such as hypertension, diabetes mellitus, and dyslipidemia, which are factors that facilitate the atherogenic process.<sup>6,16</sup> When the etiology of hypertension with renal artery stenosis is analyzed, it can be observed that atherosclerosis is responsible for approximately 90% of cases,<sup>3,4,19,20</sup> a percentage corroborated by our case series, in which 90.9% of the patients presented this etiology for renal artery stenosis. Overall, we observed that the stenosis was located in the ostium or proximal third of the renal artery and was more prevalent in the latter, which is also compatible with the literature.<sup>16,19,20</sup>

The habit of smoking alone, found in a large portion of the patients, is a significant risk factor for cardiovascular diseases, as it causes damage to the endothelial function and increased arterial rigidity and inflammation, and displaces the equilibrium between anti-thrombotic and thrombotic factors, thus favoring and accelerating the atherothrombotic process.<sup>21,22</sup> Consequently, the habit of smoking in previously hypertensive patients favors the development of

malignant and renovascular hypertension, in the case of atherosclerotic etiology, by promoting accelerated atherosclerosis.<sup>21</sup>

In hypertension with renal artery stenosis, the control of BP levels is difficult,<sup>15,23</sup> which is evidenced by the fact that, even with an average number of medications of 3.26, the patients maintained high BP levels mostly at stage II of hypertension (according to the VI Brazilian Guidelines of Hypertension<sup>9</sup>).

Along with increased tension levels, these patients have other cardiovascular risk factors such as hypercholesterolemia, hypertriglyceridemia, and smoking that, when combined, indicate an individual cardiovascular risk that is high or very high in most cases.<sup>3,4</sup> This finding can also be observed by the fact that 2/3 of the patients already met the criteria for metabolic syndrome, which reflects the presence of multiple metabolic risk factors for cardiovascular disease. Contrary to the relationship between diabetes mellitus type II and renal artery stenosis reported in the literature,<sup>5,6,8,24</sup> our patients were mostly nondiabetics.

The patients in our case series showed an average SH diagnosis time of approximately 2 decades. Furthermore, the vast majority did not show family history of SH. The low incidence of hypertension with renal artery stenosis in patients with uncomplicated SH makes it cost ineffective to screen all hypertensive patients. Thus, clinical characteristics such as the following should cause a clinician to suspect that renal artery stenosis is the cause of the patient's hypertension: SH before the age of 30 or after the age of 50; abrupt installation; symptoms or signs of atherosclerotic disease; negative family history; smoking; renal dysfunction after the use of angiotensin-converting enzyme inhibitors; recurring pulmonary edema; white race; resistance or discontinuation of therapy with diuretics and antiadrenergics; accelerated, malignant, or refractory SH; changes during physical examination such as abdominal murmurs; history of occlusive vascular disease (coronary, cerebral, peripheral); advanced fundoscopic changes; or even changes in laboratory data such as hypokalemia, proteinuria, and increased serum levels of rennin or unilateral small kidney seen on ultrasound.<sup>1,2,23</sup> Therefore, clinicians should continue their investigation to confirm the potential etiological cause.

Corroborating the observation that hypertension in patients with renal artery stenosis is usually difficult to control and that atherosclerotic disease

is a cardiovascular risk factor, it is justified that the majority of the patients in our study were in stages II and III of hypertension, used a large number of medicines without adequately controlled BP levels, and had a high or very high overall cardiovascular risk associated with metabolic syndrome and Framingham scores ranging from moderate to high risk.<sup>2,15,23,25</sup>

In addition to hypertension, renal artery stenosis (particularly of atherosclerotic etiology) may cause renal insufficiency, especially when the stenosis is bilateral, by means of chronic ischemic nephropathy.<sup>6,26</sup> This complication was also observed in our study, as some of the patients were already undergoing conservative treatment for chronic renal disease and others already presented changes in creatinine serum levels, indicating a possible unfavorable alteration in the renal function. It is estimated that approximately 12-16% of the patients with terminal chronic renal insufficiency have renal artery stenosis as the cause of their renal lesion, which causes ischemic nephropathy, especially when the stenosis is bilateral.<sup>27-29</sup>

Atherosclerotic arterial disease is a systemic disease. Finding the focus of atherosclerosis in an arterial bed indicates great predictive power of finding another focus in a concurrent location. According to the literature, the link between hypertension with renal artery stenosis of atherosclerotic origin and other atheromatous macrovascular diseases is common.<sup>30</sup> In most patients, hypertension with renal artery stenosis develops as part of systemic atherosclerotic disease and is accompanied by this condition in other vascular beds, particularly in the coronary, carotid, aortoiliac, and iliofemoral circulation.<sup>6</sup>

While reviewing the literature to develop this work, we noticed the presence of only a few articles listing the concomitance of multiartery atherosclerotic disease, in its various forms, in the same population of patients with hypertension and renal artery stenosis. Additionally, the vast majority of the studies sought to identify the incidence of renal artery stenosis in the presence of some other prior atherosclerotic disease and did not make use of the presence of renal artery stenosis to search for other more common diseases, which was the objective of this study.

Kalra *et al.*<sup>30</sup> verified in their observational study that 17.5% of the patients with hypertension and renal artery stenosis had already experienced an iEVA. In a series of patient autopsies, whose cause of death was an iEVA, Kuroda *et al.*<sup>31</sup> noted the concomitant

presence of renal artery stenosis in 10.4% of the cases. Alcázar *et al.*<sup>32</sup> found this percentage to be 27.3%, and Hans *et al.*<sup>33</sup> noted the concomitant presence of this condition in 7.2% of the patients. In our case study, we found a higher percentage than those reported (30% of patients), which could be explained by the older age of the patients in our sample.

In relation to peripheral artery disease, the concomitance with renal artery stenosis was observed with percentages between 25.8% and 44.9%.<sup>31,34-36</sup> In our study, we obtained a percentage of 16.7%, which could be explained by the fact that peripheral artery disease is more common in males,<sup>37</sup> and our case series included a majority of females.

In our study, we observed that AMI was the most common atherosclerotic disease in hypertensive patients with renal artery stenosis. Previous studies have shown that the prevalence of these comorbid conditions ranges from 11% to 30% (Jokhi *et al.*<sup>38</sup>: 30%, Kalra *et al.*<sup>30</sup>: 30.3%, Weber-Mizel *et al.*<sup>39</sup>: 18%, Handing *et al.*<sup>40</sup>: 11%, and Jean *et al.*<sup>41</sup>: 11%). The numbers in our case study (concomitance in 53.3% of the patients) was much higher than those observed in the literature, which could be explained by the high average age of the population in the study that in turn is accompanied by a higher prevalence of cardiovascular risk factors.<sup>2,15,23,25</sup> Additionally, besides being the most commonly associated atherosclerotic disease, AMI is the main cause of death in hypertensive patients with renal artery stenosis of atherosclerotic etiology.<sup>31</sup> It must also be emphasized that the patients who develop AMI may evolve to show symptoms of low chronic cardiac output, leading to exacerbation of the renal hypoperfusion syndrome, which is already in existence as a result of the hypertension due to renal artery stenosis.<sup>42,43</sup>

The mortality of hypertensive patients with renal artery stenosis of atherosclerotic origin is very high because the patients are generally elderly and because of the concomitance of the extra renal macrovascular comorbidities, particularly cardiac diseases. Furthermore, previous studies have shown that this condition alone is a major predicting factor for mortality when related to other cardiovascular diseases, especially when the stenosis is bilateral.<sup>25,30,44</sup>

Attention should be drawn to the importance of obtaining knowledge of the actual scenario in Brazil with regard to the association between hypertension

with renal artery stenosis of atherosclerotic origin and other atherosclerotic diseases. The initial characterization of this population of hypertensive patients with renal artery stenosis was the first step to creating a specific outpatient clinic for this type of hypertension in our center, which will work by establishing a partnership between the Nephrology, Vascular Surgery, and Hypertension League subject areas.

## CONCLUSION

Hypertension with renal artery stenosis of atherosclerotic origin in the study population was more common in elderly, white, and female patients, and was linked to various cardiovascular risk factors, including metabolic syndrome, with most patients having stage II/III hypertension, increased overall cardiovascular risk, and a Framingham score indicating medium risk. The most commonly associated atherosclerotic disease was AMI. These findings demonstrate that individuals with established atherosclerotic disease are at high cardiovascular risk and that all of their risk factors should be treated aggressively so that further damage can be avoided.

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