

Gender-related differences in critical limb ischemia due to peripheral arterial occlusive disease

Diferenças entre os gêneros em pacientes com isquemia crítica por doença arterial obstrutiva periférica

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Abstract

Background: Mortality from cardiovascular disease has declined among men and increased among North American women. Recent studies have revealed differences between genders in the epidemiology of atherosclerotic disease. **Objective:** To study possible differences between male and female patients with critical limb ischemia (CLI) according to risk factors of atherosclerosis and clinical characteristics of lower limbs with peripheral arterial occlusive disease (PAOD). **Methods:** The study included 171 male and female patients treated for CLI due to infrainguinal PAOD and compared clinical characteristics (Rutherford category and PAOD territory), risk factors for atherosclerosis (diabetes, age, smoking and hypertension) and number of opacified arteries on digital angiograms of the leg. The EPI-INFO software was used for statistical analysis, and the level of significance was set at $p < 0.05$. **Results:** Mean age was 70 years, and 88 patients were men (52%). For most patients (both genders), Rutherford category was 5 (82% of men and 70% of women; $p = 0.16$). The group of women had higher mean age (73 vs. 67 years; $p = 0.0002$) and greater prevalence of diabetes (66% vs. 45%; $p = 0.003$) and hypertension (90% vs. 56%; $p = 0.0000001$). Among men, the prevalence of smoking was higher (76% vs. 53%; $p = 0.0008$). The analysis of digital angiograms revealed that opacification of only one artery in the leg was found for 74% of women (vs. 50% of men). **Conclusion:** The prevalence of risk factors for atherosclerosis and the characteristics of PAOD are different between male and female patients with CLI.

Keywords: gender, atherosclerosis, ischemia; peripheral arterial disease.

Resumo

Contexto: A mortalidade por doença cardiovascular vem declinando entre os homens e aumentando entre as mulheres norte-americanas. Pesquisas mostraram diferenças relacionadas ao gênero na epidemiologia da doença aterosclerótica. **Objetivo:** Estudar possíveis diferenças entre pacientes com isquemia crítica por doença arterial obstrutiva periférica (DAOP), de ambos os gêneros, em relação à presença de fatores de risco para a aterosclerose e características da DAOP infrainguinal. **Métodos:** Foram incluídos 171 doentes internados com isquemia crítica por DAOP infrainguinal. Estudamos comparativamente, entre homens e mulheres, as características clínicas (Classificação de Rutherford e território da DAOP), a presença de fatores de risco para a aterosclerose (diabetes, idade, tabagismo e hipertensão arterial) e o número de artérias com alguma opacificação nas angiografias digitais da perna. A análise estatística foi realizada pelo EPI-INFO. Considerou-se significante $p < 0,05$. **Resultados:** Dentre os 171 casos, a média de idade foi 70 anos, sendo 88 doentes do gênero masculino (52%). A maioria dos pacientes, de ambos os gêneros, era Categoria 5 da Classificação de Rutherford (82% dos homens e 70% das mulheres/ $p = 0,16$). O gênero feminino apresentou média de idade mais avançada (73 VS 67 anos/ $p = 0,0002$), maior prevalência de diabetes (66% VS 45%/ $p = 0,003$) e de HAS (90% VS 56%/ $p = 0,0000001$). Os homens mostraram maior prevalência de tabagismo (76% VS 53%/ $p = 0,0008$). Nas arteriografias, 74% das mulheres (VS 50% homens) apresentaram opacificação de apenas uma artéria na perna. **Conclusão:** O estudo mostrou que existe diferença entre homens e mulheres com isquemia crítica em relação à prevalência dos fatores de risco para aterosclerose e às características da DAOP.

Palavras-chave: gênero; aterosclerose; isquemia; doença arterial obstrutiva periférica.

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■ INTRODUCTION

Mortality due to cardiovascular diseases (CVD), in the United States, has been declining among men and increasing among women since the 1980s¹. In Brazil, data collected in 2007 showed that over 70% of all deaths were due to noninfectious chronic diseases, such as CVD and diabetes². According to Brazilian studies, there has been an increase in overweight and obesity rates in the last decades, greater among women, which has affected the prevalence of diabetes, metabolic syndrome and CVD². Current research has investigated possible gender differences in the following diseases: ischemic heart disease, peripheral arterial occlusive disease (PAOD), abdominal aortic aneurysm and carotid atherosclerosis^{1,3-9}. Prevalence of risk factors and comorbidities may be different between men and women with PAOD¹. Patients with critical limb ischemia, characterized by pain at rest, ulcer or gangrene, secondary to peripheral vascular disease, are at a high risk of CVD and limb loss¹⁰.

This study evaluated severity of clinical conditions, PAOD territory and prevalence of atherosclerosis risk factors to determine whether there are differences between male and female patients with critical lower limb ischemia due to infrainguinal PAOD.

■ METHODS

This study included 171 consecutive patients hospitalized in Complexo Hospitalar Universitário Professor Edgard Santos of Universidade Federal da Bahia for treatment of critical lower limb ischemia due to atherosclerotic infrainguinal PAOD. This retrospective study was approved by the Ethics in Research Committee of Complexo Hospitalar Universitário Professor Edgard Santos of Universidade Federal da Bahia. Medical charts and clinical follow-up files of patients hospitalized in the Vascular Surgery Service from December 2005 to December 2011 were reviewed to collect data.

The 171 patients included in the study had been hospitalized for treatment of critical limb ischemia. Physical examination revealed normal femoral pulses, which confirmed that the obstructive disease was infrainguinal. Exclusion criteria were hospitalization due to acute ischemia, non-atherosclerotic ischemic disease, no critical ischemia at admission and/or aortoiliac PAOD.

Patients were included if their clinical data and digital subtraction arteriograms were found in the clinical follow-up files of the Vascular Service. A protocol was prepared to collect medical information. Two vascular surgeons examined arteriograms and

recorded the number of leg arteries that had any opacified segment. Patients were divided into two groups according to gender for the comparison of clinical profile, atherosclerosis risk factors and number of leg arteries with at least one opacified segment on angiograms. Patients with diabetes were those with a previous diagnosis of the disease and who were receiving treatment for it; the same criteria were used to classify patients with hypertension. For the analysis of study data, patients were classified as smokers when currently smoking.

The following factors were compared between the two groups of patients: Rutherford category of the lower extremity with critical limb ischemia¹; patient report of previous diagnosis of heart disease or chronic renal insufficiency; and territory of infrainguinal PAOD according to the examination of pulses (femoropopliteal or infrapatellar). PAOD was classified as femoropopliteal when the popliteal pulse was absent, and as infrapatellar, when the popliteal pulse was palpable and normal. The correlation between prevalence of atherosclerosis risk factors (age, hypertension, diabetes and smoking) in men and women was also analyzed. The number of arteries with at least one opacified segment in the digital arteriogram of the leg, from zero to three, was recorded.

Microsoft Excel® was used to record data, and the Epi-Info 3.3.2 software, launched in February 2005, to analyze data. To test the association between qualitative variables of atherosclerosis risk factors, a chi-square (χ^2) test was used. Quantitative variables, such as age, were compared using analysis of variance (ANOVA). The level of significance was set at 5% ($p < 0.05$) to reject the hypothesis of no difference in study variables between genders.

■ RESULTS

Eighty-eight (52%) patients were men, and 83 (48%), women. Ninety-five patients (56% of the sample) had diabetes, and 124 (73%), hypertension; 111 were current smokers. The Rutherford¹ category of chronic critical limb ischemia was 5 for 76% of the patients, 6 for 17% and 4 for 7%. The characteristics of the 171 patients are shown in Table 1. The mean duration of lesion in patients classified as Rutherford 5 or 6 before treatment was 92 days.

The comparison of the several PAOD risk factors between male and female patients revealed that women had a mean age significantly greater and a greater prevalence of diabetes and hypertension (Table 2). Men had a greater prevalence of current smoking. The risk factors (diabetes, hypertension

and smoking) were grouped and compared according to number of risk factors. Among women, 82% had two or three risk factors; among men, that rate was 64%. The analysis of PAOD territory revealed that women had a proportionally greater occurrence of femoropopliteal disease (84%) than men (Table 2). Although most men had femoropopliteal disease (66%), they had a proportionally greater occurrence of only infrapatellar occlusive lesions, with normal popliteal pulses at physical examination (34% of the cases). The severity of clinical condition, assessed

according to the Rutherford category, was not different between genders. The comparison of the male and female characteristics is shown in Table 2. Duration of ischemic lesion on the foot before hospitalization was 85 days for men and 99 days for women ($p=0.18$).

The digital subtraction arteriograms included in the study showed that 74% of the women had only one opacified artery in the leg ($p=0.005$), whereas the same was found in only 50% of the men. Only 2% of the women and 10% of the men had at least one opacified segment in any of the three leg arteries (Table 3).

Table 1. Characteristics of the 171 patients with critical limb ischemia due to peripheral arterial occlusive disease (PAOD).

Sample characteristics (171 cases)		N (%)
Gender	Male	88 (52%)
	Female	83 (48%)
Mean age		70 years
Heart disease		30 (18%)
Diabetes mellitus		95 (56%)
Hypertension		124 (73%)
Current smoking		111 (65%)
Chronic renal insufficiency		13 (8%)
PAOD territory	Femoropopliteal	128 (75%)
	Infrapatellar	43 (25%)
Rutherford	Category 4	12 (7%)
	Category 5	130 (76%)
	Category 6	29 (17%)

DISCUSSION

Cardiovascular diseases (CVD) are the main cause of death in the Brazilian population², and the study of the characteristics of patients with PAOD may help us to find epidemiological data that contribute for the development of preventive measures. Differences in CVD between genders have been described in the literature. The analysis of men and women with abdominal aortic aneurysms (AAA) revealed that women seem to have a lower percentage of collagen in the aortic wall, whereas men have a smaller amount of elastin⁴. Anatomic characteristics and mean age of men and women treated for AAA also differed in a study that followed

Table 2. Comparative analysis of male and female patients according to clinical characteristics and risk factors of peripheral arterial occlusive disease (PAOD).

Characteristic	Male (88 patients)		Female (83 patients)		p
	N (%)	N (%)	N (%)	N (%)	
Mean age	67 years	73 years			0.0002
Diabetes	40 (45%)	55 (66%)			0.003
Currently smoking	67 (76%)	44 (53%)			0.0008
Hypertension	49 (56%)	75 (90%)			0.000001
PAOD territory	Femoropopliteal	58 (66%)	70 (84%)		0.002
	Infrapatellar	30 (34%)	13 (16%)		
Number of risk factors *	0	4 (4%)	1 (1%)		0.043
	1	28 (32%)	14 (17%)		
	2	40 (46%)	44 (53%)		
	3	16 (18%)	24 (29%)		
Heart disease	16 (18%)	14 (17%)			0.41
Chronic renal insufficiency	8 (9%)	5 (6%)			0.23
Rutherford category	Category 4	4 (4%)	8 (10%)		0.16
	Category 5	72 (82%)	58 (70%)		
	Category 6	12 (14%)	17 (20%)		

*Only three risk factors were included: diabetes, hypertension and current smoking.

Table 3. Comparison of number of leg arteries visualized on digital angiograms of male and female patients with critical limb ischemia due to infrainguinal PAOD.

Number of opacified arteries*	Male (88 patients)	Female (83 patients)	p
	N (%)	N (%)	
0 (none)	3 (3%)	0 (0%)	0.005
1	44 (50%)	61 (74%)	
2	32 (37%)	20 (24%)	
3	9 (10%)	2 (2%)	

* At least one segment of leg artery (anterior tibial, posterior tibial or peroneal artery).

up patients that underwent endovascular repair⁵. Those authors evaluated the occurrence of medial-intimal thickening in the common carotid arteries and found that the difference between men and women decreased after age 65 years⁹.

In the United States, studies showed that ischemic heart disease in women occurs ten years later than in men, and that when it does, women have more associated chronic comorbidities¹. Our study found a similar trend among women with advanced PAOD. The prevalence of PAOD increases with age³. In our sample, women were a mean six years older than men and had a greater prevalence of diabetes and hypertension. Other authors found that women hospitalized due to acute myocardial infarction were older than men⁹. Lindgren et al., however, found no significant differences in mean age between patients of both genders who underwent angioplasty of the superficial femoral artery due to PAOD⁶. Those authors included patients with claudication in their sample and found a significantly higher percentage of critical ischemia among women that underwent treatment than among men⁶.

The higher prevalence of hypertension among women was also found by other authors in studies about CVD^{8,9,11}. Su et al. found an increase in the prevalence of hypertension among women after menopause⁹. In 2008, Brazilian estimates indicated that 24% of women and 17% of men older than 20 years had a diagnosis of hypertension.

Diabetes was also more prevalent among women in our sample. Fewer than half (45%) of all men had diabetes, compared to 66% of women. Diabetes, a risk factor with a high impact on atherosclerosis in women, increases the risk of CVD three to seven times among women and two to four times among men¹. CVD is more frequent among women with diabetes¹². A Brazilian study about the prevalence of chronic diabetes complications found that 58% of the 927 patients included were women, and the

overall prevalence of peripheral vascular disease was 33%¹³. The higher prevalence of diabetes among women, particularly among elderly women, has been confirmed by other authors¹¹. In contrast, two studies that evaluated patients treated for infrainguinal PAOD using an endovascular approach found no significant differences in the occurrence of diabetes among men and women^{6,7}. This sample included only patients with critical ischemia, and most had gangrene lesions in the foot, a sign of advanced PAOD and of a clinically more severe condition.

In our study, only smoking was more prevalent among men, which is in agreement with other studies that also found a greater frequency of smoking among men with peripheral and atherosclerotic carotid diseases⁶⁻⁸. As our study was retrospective, only current smoking was analyzed. We had no accurate information about the number of cigarettes or details about previous smoking habits or abstinence duration.

In the United States, two of each three women have at least one risk factor for ischemic heart disease¹. In our study, which included only cases of critical ischemia due to PAOD, women had a higher number of risk factors than men when the three main PAOD risk factors were analyzed: diabetes, hypertension and smoking. Only one or none of these three comorbidities was found for 36% of the men, but only for 18% of the women. Among patients that also had heart disease, Scherr et al. found a greater percentage of women with more than two atherosclerosis risk factors¹¹.

Our study investigated possible differences between men and women with advanced PAOD and critical ischemia and correlated gender with aspects of peripheral atherosclerotic disease, a topic about which there are few studies in the Brazilian literature. Patients with critical limb ischemia have a mortality of about 20% in the first year after disease onset¹⁰, mostly due to CVD. Only a small percentage of our male and female patients presented with a previous diagnosis of ischemic heart disease or chronic renal disease. If performed, tests to investigate CVD might have revealed a greater prevalence of undiagnosed heart disease in our sample. In Brazil, the AFIRMAR study found that the main risk factors for acute myocardial infarction are smoking, diabetes and central obesity; the first two were prevalent in our sample, which indicated that our patients had a high risk of heart disease¹⁴.

The diagnosis based on the physical examination of pulses revealed that most of our patients, in both groups, had femoropopliteal PAOD. The use of a

clinical criterion to determine PAOD territory is based on the idea that advanced superficial femoral artery disease with critical stenosis or occlusion is present when the popliteal pulse is absent. A full popliteal pulse, however, suggests that there is no hemodynamically significant stenosis of the superficial femoral artery. In addition to the clinical criterion, we evaluated angiograms and compared only data about the number of leg arteries that had at least one opacified segment. Most of our cases of femoropopliteal disease showed several opacified segments, and the femoropopliteal and infrapatellar territories were affected; only two women had opacified segments in the three leg arteries on angiograms. Clinically-diagnosed infrapatellar disease alone was proportionally more frequent among men, which indicated that a more diffuse disease, affecting both territories (femoropopliteal and infrapatellar), was found among women. Other authors suggested a more advanced degree of PAOD in women that underwent lower extremity interventions^{6,7}.

Female patients had a smaller number of arteries visualized on the leg arteriograms, and 74% of the women only had opacified segments in one of the three arteries (anterior tibial, posterior tibial or peroneal artery). Lindgren et al. studied patients that underwent invasive treatment for infrainguinal PAOD and found that women had longer atherosclerotic lesions of the superficial femoral artery and a greater tendency to need treatment of the arteries below the knee⁶. Atherosclerotic coronary lesions in women have a different anatomic pattern from that found in men and a worse prognosis¹. Nguyem et al. conducted a multicenter study and found that, among patients with critical ischemia that underwent revascularization, black women had the highest risk of limb loss¹⁵. We did not study the possible correlations between female gender and limb loss or mortality. In heart disease, prognostic differences associated with gender may be secondary to greater prevalence of diabetes, obesity and dyslipidemia among women¹. The loss of protections against heart disease among older women may be correlated with a fall in estrogen levels¹². Studies show an acceleration of atherosclerotic disease after menopause and an increase of CVD risk factors in women older than 55 years⁹.

Some of the limitations of this study are to its retrospective design and the fact that data about body mass index, dyslipidemia and laboratory test results, such as LDL levels, were not collected. Despite those limitations, our findings revealed differences

between male and female patients with advanced chronic peripheral ischemic disease according to their clinical profiles (age, hypertension, diabetes). Future studies should further investigate the consequences of such differences between genders in PAOD and their possible impact on prognosis.

In conclusion, our findings suggest that clinical severity of atherosclerotic limb disease, defined according to Rutherford category, does not differ between men and women with critical limb ischemia, but women are older and have a more diffuse atherosclerotic disease. Also, in the group of patients with critical limb ischemia due to PAOD, diabetes and hypertension are more prevalent among women, whereas current smoking is more frequent among men.

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