CLINICAL SCIENCE

Carotid stenosis: what is the high-risk population?

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OBJECTIVE: Prevention is the best treatment for cerebrovascular disease, which is why early diagnosis and the immediate treatment of carotid stenosis contribute significantly to reducing the incidence of stroke. Given its silent nature, 80% of stroke cases occur in asymptomatic individuals, emphasizing the importance of screening individuals with carotid stenosis and identifying high-risk groups for the disease. The aim of this study was to determine the prevalence and the most frequent risk factors for carotid stenosis.

METHODS: A transversal study was conducted in the form of a stroke prevention campaign held on three non-consecutive Saturdays. During the sessions, carotid stenosis diagnostic procedures were performed for 500 individuals aged 60 years or older who had systemic arterial hypertension and/or diabetes mellitus and/or coronary heart disease and/or a family history of stroke.

RESULTS: The prevalence of carotid stenosis in the population studied was 7.4%, and the most frequent risk factors identified were mean age of 70 years, carotid bruit, peripheral obstructive arterial disease, coronary insufficiency and smoking. Independent predictive factors of carotid stenosis include the presence of carotid bruit or peripheral obstructive heart disease and/or coronary insufficiency.

CONCLUSIONS: The population with peripheral obstructive heart disease and carotid bruit should undergo routine screening for carotid stenosis.

KEYWORDS: Carotid Stenosis; Risk Factors; Early Diagnosis.

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INTRODUCTION

In 2004, the Atlas of Heart Disease and Stroke published by the World Health Organization registered a total of 129,172 deaths as a result of stroke in Brazil (1). The same publication reported that approximately 15 million people suffer from stroke annually worldwide, and 5.5 million of them die as a result of the disease.

Ischemic stroke accounts for 67% to 83% of all strokes (2). It can be caused by carotid artery disease, cardiac arrhythmia and arterial hypertension (3). Extracranial cerebrovascular disease stems from atherosclerotic lesions located predominantly in the carotid bifurcation and are responsible for up to 75% of ischemic stroke events (2). These lesions can cause cerebral ischemia via the embolization of atheromatous plaques, the formation of thrombi or arterial occlusion. However, this type of lesion is easily diagnosed with non-invasive methods and can be managed with effective therapeutic options (4).

Barnett et al. (5) estimated that approximately two million North Americans and Europeans have treatable asymptomatic carotid artery stenosis. Roederer et al. (6) estimated the risk of stroke or total carotid occlusion at 46% per year in patients with asymptomatic carotid stenosis greater than or equal to 80%. According to Chambers et al. (7), individuals with carotid stenosis greater than or equal to 75% have a 26% risk of developing stroke in three years.

Given its silent nature, 80% of stroke cases occur in asymptomatic individuals (8), hence the importance of screening individuals with carotid stenosis and identifying groups at high risk for the disease. Moreover, the annual progression of moderate to severe stenosis is 14% (9).

Few studies have focused on determining the prevalence of carotid stenosis in the general population because the operational costs of routine screening are high. Nevertheless, the estimated prevalence of carotid stenosis greater than or equal to 50% in the general population ranges from 2 to 8%, and the estimated prevalence of stenosis greater than or equal to 80% ranges from 1 to 2% (10). Therefore,

No potential conflict of interest was reported.

studies have attempted to identify a high-risk population that would benefit from the early diagnosis of carotid stenosis.

According to Yin and Carpenter (11), screening asymptomatic individuals is only cost-effective in populations presenting with the following characteristics: carotid stenosis prevalence greater than 4.5%; echo Doppler specificity greater than 91%; stroke incidence during clinical treatment greater than 3.3%; reduction in stroke risk greater than 37%; and occurrence of stroke associated with carotid endarterectomy consistent with the rates published by NASCET and ACAS. Furthermore, the operational cost per exam must be less than US$300.

According to a committee of the American Society of Neuroimaging (12), cost-effective screening lowers the stroke risk when the carotid stenosis prevalence is between 5% and 20%, and screening does not reduce stroke risk and is not cost-effective when the carotid stenosis prevalence is lower than 5%.

In Brazil, no screening studies in this patient group have been conducted for the general population or a selected population. This lack of studies informed the rationale for this study, which sought to contribute to a deeper understanding of the role of carotid stenosis screening in populations at risk for atherosclerosis, to determine the prevalence of the disease and to characterize the population at high risk of developing the disease.

METHODS

This study was previously approved by the Research Ethics Committee under Project No. 469/07.

The Department of Vascular and Endovascular Surgery conducted a transverse study in the form of a stroke prevention campaign in May and June 2004. The campaign was publicized through pamphlets, flyers displayed on newsstands and at pharmacies and bakeries and via radio broadcasts and advertisements in local newspapers in downtown São Paulo city.

The campaign was run on three non-consecutive Saturdays. Carotid stenosis diagnosis sessions were offered to interested individuals who were aged 60 years or older and who were diagnosed with one of the following conditions: systemic arterial hypertension, diabetes mellitus, coronary heart disease or familial history of stroke. These factors constituted the study's inclusion criteria.

Interested individuals were asked to call the telephone number provided and to schedule a day and time for an interview and exam.

A total of 632 interviews were scheduled by phone. Of these, 582 individuals participated in the scheduled interviews. Eighty-two volunteers did not meet the campaign criteria and were excluded from the study. The final sample consisted of 500 individuals.

The interviews were conducted by eight physicians from the Department of Vascular and Endovascular Surgery, who administered a predetermined questionnaire addressing the health history and familial morbid antecedents of each volunteer. A physical exam was then performed to check for carotid bruit, palpate the pulses of the extremities and take blood pressure readings.

After the interview and physical exam, the volunteers were referred for an ultrasonography exam with Doppler (Prologic 7 device by GE - Waukesha, USA and SD800 device by Phillips - Amsterdam, Netherlands) to detect occult carotid stenosis, according to the model proposed by Jacobowitz et al. (2,13). This scan consists of a modified ultrasonographic exam, which has been regularly validated and compared with angiography and angioresonance as part of an accreditation by the Intersocietal Commission for the Accreditation of Vascular Laboratories (ICAVL). The test consists of an examination of the distal common carotid artery and the bulb and proximal segments of the internal and external carotid arteries, including the determination of peak systolic velocities in the internal carotid artery. A velocity greater than or equal to 120 cm/s is considered to indicate the presence of >50% stenosis. In addition to this criterion, the common and internal carotid arteries underwent a morphological analysis that classified them as normal, narrowed, less than 50% stenosis, or greater than 50% stenosis.

Ultrasound exams were conducted by three radiologists specializing in vascular ultrasonography. All positive results were subsequently confirmed by a second examiner.

The volunteers were split into two groups based on the ultrasound exam findings:

- Positive: Internal carotid artery stenosis ≥50%
- Negative: Internal carotid artery stenosis <50%

The groups were then analyzed for the following variables:

- Age
- Gender
- Race
- Arterial hypertension (SAH): Systolic arterial pressure ≥140 mmHg and/or diastolic ≥90 mmHg (14) or chronic use of anti-hypertensive medication;
- Diabetes mellitus (DM) with a fasting glucose exam ≥126 mg/dL (15) or the use of oral hypoglycemics or insulin;
- Dyslipidemia: Cholesterol levels ≥200 mg/dL or LDL levels ≥130 mg/dL or triglyceride levels ≥150 mg/dL (16) or the use of statins or fibrates;
- Peripheral obstructive arterial disease (POAD): The absence of pulses in the extremities, confirmed by a second examiner;
- Coronary insufficiency (CI): The presence of stable or unstable angina, history of myocardial infarction, myocardial revascularization or coronary angioplasty;
- Other cardiopathies, such as arrhythmias, valvulopathies, congestive cardiac insufficiency or the use of a pacemaker or an internal cardioverter defibrillator;
- Smoking: Current smokers who have smoked at least 100 cigarettes throughout their lifetime (17);
- Signs and symptoms of a cerebral ischemic event: Asymptomatic, syncope, transient ischemic attack or stroke (amaurosis fugax, aphasia or dysphasia and motor deficit);
- Family history of stroke in first-degree relatives;
- Presence of carotid bruit based on auscultation of the cervical region at the medial border of the sternocleidomastoid muscle with a stethoscope.

A 5% level of significance was adopted. Values expressed in frequencies were compared using the chi-squared test and its variations (Fisher's exact test and a generalization of

Fisher's exact test for tables with low frequencies). Special attention was given to the variable "carotid bruit", which was treated as a dependent variable.

The Student's t test, controlled by Levene's test, was used to compare continuous values.

A logistic regression analysis was used to determine the relationship between the study variables and exam results. The regression model was tested by selecting the variables that were significant at a level of 10% in a univariate analysis ($p<0.100$).

The data were tabulated and analyzed using the SAS 9.1 software program.

RESULTS

The characteristics of the study sample are shown in Table 1.

Ultrasound examinations revealed positive results (i.e., ≥50% carotid stenosis) in 37 individuals, representing 7.4% of the population assessed.

When positive and negative carotid stenosis results were compared by subjects' ages, the mean age of the positive group (70.4±6.8 years) was statistically significantly higher than that of the negative group (67.5±6.3; $p=0.01$). However, no statistical differences in gender or race were detected between the carotid stenosis-positive and negative groups.

Table 2 presents a comparison of the carotid stenosis-positive and negative groups in terms of the presence of risk factors for atherosclerosis. The results indicate that only the variables PAOD, Smoking and CI are individual risk factors for internal carotid artery stenosis >50%.

Regarding cerebral ischemia symptoms, no statistically significant differences were observed between the carotid stenosis-positive and negative groups in terms of reported syncope, motor sequelae or amaurosis fugax.

Ten individuals (2%) tested positive for carotid bruit (Table 3). Carotid bruit was identified in 50% of the subjects in the positive group, while only 7.1% of the individuals without carotid bruit had significant stenosis of the carotid artery.

No statistically significant association was observed between the sum of the risk factors and an increased prevalence of carotid stenosis (Table 4).

Based on the model containing the six most significant variables that were identified during the univariate analysis, we concluded that the presences of bruit and POAD are predictors of carotid stenosis ($p<0.05$).

The presence of cardiac bruit increased the probability of a positive exam result 12-fold (OR = 12.6) and that POAD increased the likelihood of a positive result 3-fold (OR = 3.7) compared to the chance of positivity when these factors were absent (Table 5).

The variable ''coronary insufficiency'' had a descriptive level of approximately 5% ($p=0.045$). Taking this level as significant, we can conclude that, on average, the likelihood of a positive ultrasound result is doubled in the presence of angioplasty, coronary artery bypass or angina compared to the absence of these conditions (OR = 2.3).

Table 5 shows the most frequent variables associated with a positive ultrasound result.

Table 1 - Characterization of a sample of 500 participants in the Stroke Prevention Campaign who underwent carotid stenosis screening.

	Total	
Age (years)		
Mean ± S.D.	67.8 ± 6.4	
Median	66.0	
Minimum-maximum	60–89	
Gender - n (%)		
Female	279	(55.8%)
Male	221	(44.2%)
Race - n (%)		
White	413	(82.6%)
Black	60	(12.0%)
Yellow	27	(5.4%)
Signs and symptoms of stroke - n (%)		
Asymptomatic	255	(51.0%)
Visual symptoms	57	(11.4%)
Syncope	53	(10.6%)
Sequelae	18	(3.6%)
Variables - n (%)		
SAH	364	(72.8%)
Dyslipidemia	250	(50.0%)
Family history of stroke	215	(43.0%)
Smoking	182	(36.4%)
CI (angina, angioplasty or coronary artery bypass)	122	(24.4%)
DM	116	(23.2%)
PAOD	107	(21.4%)
Cardiopathy	90	(18.0%)
Bruit	10	(2.0%)
Total	500	(100.0%)

SAH: Arterial hypertension; CI: Coronary insufficiency; DM: Diabetes mellitus; PAOD: Peripheral obstructive arterial disease.

DISCUSSION

The diagnostic method employed in this study was ultrasonography with Doppler using a modified version of the approach described by Jacobowitz et al. (8). The cut-off value adopted was close to the value recommended by Carsen III et al. (18), who observed optimal sensitivity (91%), specificity (95%), positive predictive value (89%) and negative predictive value (96%) with a cut-off of 115 cm/s in screening exams that took an average of 3.2 minutes to perform per patient.

In this population-based study, the prevalence of >50% stenosis of the internal carotid artery was 7.4%.

The prevalence of significant asymptomatic carotid stenosis (≥50%) varies. Prevalences between 4 and 8% were found in the general population, with advanced age being the only independent predictor of significant asymptomatic carotid stenosis (8,9). In contrast, the values reported by Qureshi et al. (12) ranged from 7% to 35%, depending on the isolated or associated presence of such risk factors as age over 65 years, smoking, coronary insufficiency, and hypercholesterolemia.

In this study, no statistical significances were identified for the variables gender, race, SAH, DM, dyslipidemia, cardiopathies, familial history of stroke, or cerebral ischemia symptoms. Similarly, the sum of the risk factors did not predict carotid stenosis.

In terms of gender, the literature only reports a statistically significant difference when analyzing specific subgroups, such as candidates for myocardial revascularization (greater risk among women) (19) or individuals with POAD

Table 2 - Comparison of variables considered risk factors for atherosclerosis between the groups that were positive and negative for carotid stenosis on ultrasound.

Presence of risk factors for atherosclerosis	Ultrasound		*p*-value
	Negative	Positive	
SAH			$p = 0.054$
No	**130 (96.3%)**	**5 (3.7%)**	
Yes	**333 (91.2%)**	**32 (8.8%)**	
DM			$p = 0.147$
No	352 (91.7%)	32 (8.3%)	
Yes	111 (95.7%)	5 (4.3%)	
Dyslipidemia			$p = 0.393$
No	229 (91.6%)	21 (8.4%)	
Yes	234 (93.6%)	16 (6.4%)	
PAOD			$p<0.001$*
No	369 (94.4%)	22 (5.6%)	
Yes	91 (83.5%)	18 (16.5%)	
CI			$p = 0.002$*
No	358 (94.7%)	20 (5.3%)	
Yes	105 (86.1%)	17 (13.9%)	
Cardiopathy			$p = 0.237$
No	377 (92.0%)	33 (8.0%)	
Yes	86 (95.6%)	4 (4.4%)	
Smoking			$p = 0.020$*
No	300 (94.3%)	18 (5.7%)	
Yes	163 (89.6%)	19 (10.4%)	
Family history of stroke			$p = 0.315$
No	261 (91.6%)	24 (8.4%)	
Yes	202 (94.0%)	13 (6.0%)	

(greater risk among men) (20). No reports were found that described differences related to race (2,8,10).

The percentage of patients with SAH was significantly higher in the group that tested positive for >50% carotid stenosis, although SAH was not an independent predictor. This finding contrasts with some authors' results (2,8) but corroborates the observations of Qureshi et al. (12), indicating that isolated SAH should not be used as a marker for screening asymptomatic carotid stenosis.

The presence of DM was not significantly correlated with carotid stenosis. This finding is consistent with the majority of previous scientific studies, although DM is regarded as a risk factor in the pathogenesis of atherosclerosis (9,10,21).

The presence of dyslipidemia did not predict carotid stenosis in this study, corroborating the results of most studies in the literature (2,8,9,20,22).

Univariate analysis showed that of the variables studied, advanced age, smoking, POAD, and CI were predictors of carotid stenosis.

The direct relationship between age and carotid stenosis risk has been confirmed by several previous studies (9,10,21,23,24), and our results corroborated this finding.

Table 3 - Comparison of the presence of carotid bruit and carotid stenosis findings on ultrasound.

	Ultrasound		Total	*p*-value
	Negative	Positive		
Bruit - n (%)				$p<0.001$
No	455 (92.9%)	35 (7.1%)	490 (100.0%)	
Yes	5 (50.0%)	5 (50.0%)	10 (100.0%)	
Total patients	460 (92.0%)	40 (8.0%)	500 (100.0%)	

p-value: Fisher's exact test.

Smoking is considered one of the most important risk factors in the genesis of atherosclerosis. However, there is a lack of consensus in the literature regarding the predictive value of the association between smoking and carotid stenosis. Some authors have confirmed this link (2,9,10), while others have failed to observe a statistically significant association. In this study, smoking was reported in 51% of the carotid stenosis-positive group. While the univariate analysis revealed that smoking was a predictive factor for carotid stenosis, the association was not significant in the subsequent multivariate analysis.

Consistent with our findings, several studies have identified both POAD (20,24,25) and CI (2,10,12,20) as independent predictors for significant asymptomatic carotid stenosis.

In male populations with POAD, a carotid stenosis prevalence of 18% was detected in young adults (20), and a 20% prevalence was identified in elderly adults (25). CI was found to be a predictive factor for >50% carotid stenosis in both of these groups, especially the younger group (19,25). In a Chinese population, this prevalence

Table 4 - Association between the number of risk factors and the presence of carotid stenosis on ultrasound.

	Ultrasound		Total	*p*-value
	Negative	Positive		
No. of risk factors – n (%)				$p = 0.064$
1	78 (97.5%)	2 (2.5%)	80 (100.0%)	
2	122 (94.6%)	7 (5.4%)	129 (100.0%)	
3 or more	263 (90.4%)	28 (9.6%)	291 (100.0%)	
Total patients	463 (92.6%)	37 (7.4%)	500 (100.0%)	

p-value: Fisher's exact test.

Table 5 - Logistic regression analysis for the most frequently occurring variables and positive ultrasound findings.

	OR[1] (score estimate)	OR[1] - Confidence interval (95%)	*p*-value
Variables:			
Bruit	12.6	[2.8; 55.6]	0.001*
PAOD	3.7	[1.7; 8.1]	0.001*
CI	2.3	[1.0; 5.0]	0.045*
SAH	2.4	[0.8; 6.8]	0.116
Smoking	1.4	[0.9; 2.2]	0.133
No. of risk factors	0.9	[0.6; 1.4]	0.671

SAH: Arterial hypertension; CI: Coronary insufficiency; DM: Diabetes mellitus; PAOD: Peripheral obstructive arterial disease.
p-value (model) <0.0001; N = 500; [1]OR = odds ratio.

reached 24.7%, and risk factors included advanced age, carotid bruit and smoking, with a particular emphasis on the number of cigarettes smoked per day (24).

A study involving 168 patients with atherosclerotic aortoiliac disease identified a 28% prevalence of significant carotid stenosis; advanced age and the presence of carotid bruit were predictors of more severe stenoses in this population (26).

The close relationship between carotid stenosis and coronary heart disease has been recognized, as the diseases share the same risk factors and pathogenic mechanisms. The literature indicates that the prevalence of CI in patients with extracranial cerebral disease ranges from 40% to 60%, and the carotid disease rate in candidates for myocardial revascularization ranges from 2 to 27%, based on a review of 12 studies published between 1983 and 1996 (27). The 13.9% prevalence of ≥50% carotid stenosis among individuals with CI in this study is consistent with the rate reported in the literature.

Several studies have reported a positive relationship between cervical bruit and carotid stenosis (28,29). According to the ACAS, ipsilateral bruit was detected in 75% of individuals with ≥60% carotid stenosis, suggesting that 80% of patients with significant carotid disease had carotid bruit.

Some screening programs have identified carotid bruit as a strong predictor of carotid stenosis, particularly among men with PAOD (24,25). Our results found that 50% of individuals with ≥50% carotid stenosis had carotid bruit; its sensitivity as a predictor was 50%. Lavenson Jr. et al. (30) screened 176 individuals to validate a stroke prevention protocol and found a carotid bruit rate similar to that identified in this study. Despite its low sensitivity, the presence of carotid bruit proved highly specific for the occurrence of carotid stenosis, yielding a negative predictive value of 0.99.

Two other studies also aimed to determine the population that would benefit most from carotid stenosis screening. The first of these studies (8) included 394 individuals and found a carotid stenosis prevalence ranging between 1.8% (no risk factors) and 66.7% (four associated risk factors). Heart disease and arterial hypertension have been determined as predictors of significant asymptomatic carotid stenosis. However, this study failed to confirm this association between the number of risk factors and an increased prevalence of carotid stenosis.

In the second study (2), 610 individuals were screened. A 10.8 % prevalence of carotid stenosis was found, indicating a strong correlation with CI. Our screening study revealed a lower prevalence (7.4%), but CI was also found to be an independent predictor of >50% carotid stenosis.

Among the studied risk factors for atherosclerotic disease, the presence of carotid bruit, PAOD, advanced age, CI and smoking were significantly correlated with a diagnosis of >50% carotid stenosis in univariate analyses. However, a multivariate logistic regression analysis only identified correlations between carotid stenosis and carotid bruit, PAOD and CI, which were determined to be significant independent risk factors for carotid stenosis. The results of relative risk calculations confirmed the association between stenosis and carotid bruit.

Conclusive studies to determine the cost-benefit of this screening are needed. Although the prevalence of asymptomatic carotid stenosis was significant in the population studied (7.4%) and was consistent with the recommendations by Yin and Carpenter (11), the cost of each confirmed diagnosis in this study was US$ 358.00. The acceptable recommended cost is approximately US$ 300.00 per positive diagnosis.

The adoption of more specific criteria, such as those employed in this study, combined with the introduction of portable ultrasonography equipment may increase the cost-effectiveness of carotid stenosis screening and may increase physicians' awareness of the importance of identifying high-risk individuals for stroke prevention.

The prevalence of carotid stenosis in the studied population was 7.4%, and the most frequent risk factors identified were a mean age of 70 years, carotid bruit, peripheral obstructive arterial disease, coronary insufficiency and smoking.

Independent predictive factors of carotid stenosis include the presence of carotid bruit or peripheral obstructive heart disease and/or coronary insufficiency. Populations that meet these criteria should undergo routine screening for carotid stenosis.

AUTHOR CONTRIBUTIONS

Park JH contributed to the final revision of the manuscript, collected data, conceived the study project and conducted the literature review. Razuk A, Castelli Junior V and Caffaro RA contributed to the final revision of the manuscript and conceived the study project. Saad PF contributed to the final revision of the manuscript, collected data, and conducted the literature review. Telles GJ, Rodrigues AC, Volpiani GG, Campos P and Yamada RM contributed to the final revision of the manuscript and collected data. Karakhanian WK contributed to the final revision of the manuscript and conducted the literature review. Fioranelli A contributed to the final revision of the manuscript.

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