



# High prevalence of intracranial arterial stenosis among acute ischemic stroke patients in a Brazilian center: a transcranial color-coded duplex sonography study

## *Alta prevalência de estenose arterial intracraniana nos pacientes com acidente vascular isquêmico agudo em um centro brasileiro: um estudo com Doppler transcraniano colorido*

Letícia Januzi de Almeida Rocha<sup>1,3</sup> Maria Clara Zanon Zotin<sup>2</sup> Renata da Silva Almeida Santos<sup>3</sup>  
Milena Carvalho Libardi<sup>4</sup> Millene Rodrigues Camilo<sup>3</sup> Clara Monteiro Antunes Barreira<sup>3</sup>  
Pedro Telles Cougo Pinto<sup>3</sup> Suleimy Cristina Mazim<sup>3</sup> Daniel Giansante Abud<sup>3</sup>  
Octavio Marques Pontes Neto<sup>3</sup>

<sup>1</sup> Universidade Federal de Alagoas, Hospital Universitário Professor Alberto Antunes – EBSERH, Unidade do Sistema Neurológico, Maceió AL, Brazil.

<sup>2</sup> Universidade de São Paulo, Departamento de Imagens Médicas, Hematologia e Oncologia Clínica, Ribeirão Preto SP, Brazil.

<sup>3</sup> Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Departamento de Neurociências e Ciências do Comportamento, Ribeirão Preto SP, Brazil.

<sup>4</sup> Universidade Federal de São Carlos, Hospital Universitário Professor Dr. Horácio Carlos Panepucci – EBSERH, São Carlos SP, Brazil.

**Address for correspondence** Letícia Januzi de Almeida Rocha (email: leticiajanuzi@usp.br).

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### Abstract

#### Keywords

- ▶ Ischemic Stroke
- ▶ Ischemic Attack, Transient
- ▶ Intracranial Arterial Diseases
- ▶ Ultrasonography, Doppler, Transcranial

**Background** There is limited data available regarding the prevalence of intracranial arterial stenosis (ICAS) among acute ischemic stroke (AIS) patients in Brazil and Latin America.

**Objective** The present study sought to investigate the frequency and predictors of ICAS among patients with AIS or transient ischemic attack (TIA) in a Brazilian center, with transcranial color-coded duplex sonography (TCCS) technique.

**Methods** Consecutive AIS and TIA patients, admitted to an academic public comprehensive stroke center in Brazil from February to December 2014, evaluated by TCCS were prospectively selected. Vascular narrowings > 50% were considered as ICAS, based on ultrasound criteria previously defined in the literature.

**Results** We assessed 170 consecutive patients with AIS or TIA, of whom 27 (15.9%) were excluded due to an inadequate transtemporal acoustic bone window. We confirmed ICAS in 55 patients (38.5%). The most common location was the proximal

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segment of the middle cerebral artery (28.2%), followed by the vertebral (15.4%), posterior cerebral (13.6%), terminal internal carotid (9.1%) and basilar (8.2%) arteries. On multivariate models adjusting for potential confounders, systolic blood pressure (OR: 1.03, 95%CI: 1.01–1.04;  $p = 0.008$ ) was independently associated with ICAS.

**Conclusion** We found significant ICAS in approximately 1/3 of patients admitted with symptoms of AIS or TIA in a public tertiary academic stroke center in Brazil. The TCCS is an accessible and noninvasive technique that can be used to investigate the presence of moderate and severe ICAS, especially in patients who cannot be exposed to more invasive exams, such as the use of intravenous contrast agents.

## Resumo

**Antecedentes** Dados acerca da prevalência da estenose arterial intracraniana (EAIC) entre os pacientes com acidente vascular isquêmico (AVCi) agudo no Brasil e América Latina são limitados.

**Objetivo** O presente estudo pretendeu investigar a frequência e os preditores da EAIC nos pacientes AVCi ou ataque isquêmico transitório (AIT) em um centro brasileiro utilizando o Doppler transcraniano colorido (duplex transcraniano).

**Métodos** Pacientes consecutivos com AVCi ou AIT, admitidos entre fevereiro e dezembro de 2014 em um centro acadêmico brasileiro especializado em doenças cerebrovasculares, foram avaliados prospectivamente com duplex transcraniano. Os estreitamentos vasculares  $> 50\%$  foram considerados como EAIC, baseado em critérios ultrassonográficos definidos previamente na literatura.

**Resultados** Foram avaliados 170 pacientes com AVCi ou AIT, dos quais 27 (15,9%) foram excluídos em decorrência da janela óssea transtemporal acústica inadequada. Confirmamos EAIC em 55 pacientes (38,5%). A localização mais comum foi o segmento proximal da artéria cerebral média (28,2%), seguida pelas artérias vertebral (15,4%), cerebral posterior (13,6%), carótida interna terminal (9,1%) e basilar (8,2%). No modelo multivariado, ajustado para os potenciais confundidores, a pressão arterial sistólica aumentada (OR: 1,03; IC 95%: 1,01–1,04;  $p = 0,008$ ) foi independentemente associada a EAIC.

**Conclusão** Foi identificada EAIC significativa em quase 1/3 dos pacientes admitidos com sintomas de AVCi ou AIT em um serviço acadêmico público de atendimento especializado em doenças cerebrovasculares. O Doppler transcraniano colorido é uma ferramenta acessível e não invasiva que pode ser utilizada com segurança para a investigação da presença de EAIC moderada ou grave, especialmente nos pacientes que não podem ser expostos a exames complementares mais invasivos com uso de contraste intravenoso.

## Palavras-chave

- ▶ AVC Isquêmico
- ▶ Ataque Isquêmico Transitório
- ▶ Doenças Arteriais Intracranianas
- ▶ Ultrassonografia Doppler Transcraniana

## INTRODUCTION

Intracranial arterial stenosis (ICAS) is still considered the most significant cause of acute ischemic stroke (AIS) worldwide.<sup>1</sup> However, its prevalence in Latin America is largely unknown and variable in different study methodologies and scenarios.<sup>2</sup> In Brazil, data about ICAS frequency within the AIS and TIA populations is insufficient. Patients with ICAS, particularly those with symptomatic stenosis, have a higher risk of recurrent stroke, especially during the first year after the initial stroke.<sup>3</sup> Therefore, it is essential to identify these symptoms promptly in AIS or TIA patients. Furthermore, patients with more than 50% luminal stenosis should be followed closely by aggressive secondary stroke prevention strategies.<sup>4</sup>

Techniques such as digital subtraction (DSA), computed tomographic (CTA), and magnetic resonance (MRA) angiographies are commonly used in developed countries for the

diagnosis of ICAS in AIS/TIA patients, but they have limitations such as invasiveness, high cost, contrast toxicity, and high-magnetic field restrictions. Moreover, the low availability and high cost of these modalities in developing countries may also limit their use as routine workup of ICAS as part of the diagnostic assessment of AIS patients, contributing to underestimating the burden of this condition in Brazil.<sup>5</sup> Alternatively, among neuroimaging methods, transcranial color-coded duplex sonography (TCCS) study is a noninvasive, broadly available, and inexpensive method for assessing intracranial blood flow and hemodynamic changes.<sup>6,7</sup> It is mainly used for the detection of hemodynamically significant ICAS in acute stroke patients. This study aimed to evaluate the frequency and severity of ICAS in patients with AIS and TIA admitted to an academic tertiary stroke center in Brazil using TCCS.

## METHODS

### Population and inclusion criteria

The study population consisted of all consecutive patients above 18-years-old who were admitted with AIS or TIA and evaluated by TCCS as part of their routine stroke etiologic investigation, selected prospectively from February 2014 to December 2014. During the study period, investigation of the intracranial vasculature using an imaging technique (TCCS or CTA) as part of the routine investigation of all patients suspected of having a stroke. The ethical committee of the Hospital das Clínicas from the Ribeirão Preto Medical School approved this study, and written informed consent was required from all participants. Patients without TCCS in their routine investigation, or those with bilateral inadequate trans-temporal acoustic bone window, defined as the absence of visualization of the midbrain and sphenoid wing bone by TCCS on B-mode, as well as those in whom no vascular structure could be identified, were excluded from the study.<sup>8,9</sup>

### Study protocol

The diagnosis of AIS or TIA was performed by an experienced stroke neurologist based on the patients' clinical history, neurological examination, and neuroimaging results. Symptomatic ICAS was defined as the narrowed artery being responsible for new symptoms or ischemia in the corresponding brain region.<sup>10</sup>

The data collected included demographic information, clinical history, and diagnostic workup. On admission, the national institutes of health stroke scale (NIHSS) was used to assess stroke severity, and the modified Rankin scale (mRS) was used to assess functional outcome at discharge and 90 days after the cerebrovascular event.<sup>11-13</sup>

The personal history of main risk factors for stroke was collected: systemic arterial hypertension, diabetes mellitus, smoking, alcoholism, dyslipidemia, elevated body mass index, atrial fibrillation, and prior occurrence of myocardial infarction, cerebral infarction, and TIA. Blood pressure, capillary glycemia, glycosylated hemoglobin, hemoglobin, hematocrit, and cholesterol levels were also recorded on admission. The definition of the presence of each risk factor was based on the guidelines in force at the time of data collection, as well as on the results of laboratory and imaging tests in the study protocol.

Complementary exams were performed to determine the AIS subtype according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST).<sup>14</sup>

### Imaging evaluation

#### *Transcranial color-coded duplex sonography (TCCS) study*

A TCCS study was conducted to investigate the presence and severity of ICAS in each target vessel, indicated below. All exams were performed by just one experienced neurosonographer within seven days of hospital admission using a Xario SSA-660A (Toshiba Corp. Tokio, Japan) 2MHz probe.

The study measured the maximum mean flow velocities (MFV) of the following arteries bilaterally: terminal internal

carotid artery (TICA), proximal segments (M1 and M2) of the middle cerebral artery (MCA), the anterior cerebral artery (ACA), and the P1 and P2 segments of the posterior cerebral artery (PCA). The vertebral (VA) and basilar (BA) arteries were assessed through suboccipital window.<sup>15</sup>

According to the institutional protocol data were recorded at 0° and corrected by aligning the insonation angle parallel to the blood flow vector whenever necessary.

Ultrasound investigation of cervical carotid and vertebral arteries was also performed through TCCS. If significant stenosis (70%) was found, the patient was excluded from the study as it could interfere with the analysis.

#### *Intracranial arterial stenosis (ICAS) criteria*

The following MFV cutoffs on TCCS were used for identification of hemodynamically significant stenosis ( $\geq 50\%$  luminal stenosis) according to the previous criteria, established through TCCS ultrasound examination:<sup>16,17</sup> MCA-MFV  $> 100$  cm/s, TICA MFV  $> 90$  cm/s, VA and BA MFV  $> 80$  cm/s, ACA  $> 80$  cm/s, and PCA  $> 50$  cm/s. When the absolute value of velocity did not achieve the criterion, the degree of stenosis was estimated as  $(1 - [MV \text{ pre- or post-stenotic} / MV \text{ intrastenotic}] \times 100)$ .

Having met the prerequisite of adequate quality of the ultrasound window, we defined occlusion by absent or minimal signals and sub occlusion by blunted signals. We checked all vessels every 2mm of their path, as the possibility of tortuosity could make the examination difficult and simulate occlusion. We also excluded patients with significant cervical ICAS.

In order to confirm the degree of stenosis by TCCS, we compared their findings with CTA, if this test was available, with exams being performed using a Sensation 64 machine (Siemens AG, Erlangen, Germany) and analyzed by experienced radiologist, blinded to the TCCS results, using the Osirix (Bernex, Switzerland) v.6.0.2 imaging software.

### Statistical analysis

All analyses were conducted using the Statistical Package Social Sciences (SPSS, IBM Corp., Armonk, NY, USA) version 20.0. Univariate analysis was performed using the Student t, Mann-Whitney U, Chi-squared, or Fisher exact test, as appropriate. Variables with a  $p$ -value of less than 0.1 were included in the multivariate analysis. Multivariate logistic regression (backward selection method) was then used to identify independent predictors of stenosis. A  $p$ -value of less than 0.05 (2-sided) was considered statistically significant. We evaluated the Cohen Kappa, sensitivity, specificity, and positive and negative predictive values to compare the performance of TCCS with CTA.

## RESULTS

We examined 170 subjects, of which 27 (15.9%) were excluded from the study because of inadequate acoustic trans-temporal bone windows for TCCS. These patients were similar in baseline characteristics to those with adequate transcranial windows. Of the 143 remaining patients, 89 (62.2%) were men, and 62.9% were White. The mean age was

63.6 ± 11.1 years. Furthermore, 124 (86.7%) participants had AIS, and 19 (13.3%) had TIA. The sample demographic and clinical details are displayed in ►Table 1.

The TCCS detected ICAS in 55 (38.5%) patients, and 36 (65.5%) were considered symptomatic. Male sex ( $p = 0.09$ ), NIHSS ( $p = 0.004$ ), systolic blood pressure on admission ( $p < 0.001$ ), TOAST classification ( $p < 0.0001$ ), and high-density lipoprotein (HDL) cholesterol ( $p = 0.02$ ) had an associa-

tion (►Tables 1 and 2). Increased systolic blood pressure on admission was the only factor independently associated with ICAS in the final multivariate logistic regression models (OR: 1.02; 95% confidence interval [CI]: 1.01–1.05;  $p = 0.008$ ), as shown in ►Table 3.

The frequency of ICAS according to the different locations in proximal arteries is given in ►Table 4. The number of ICAS vessels was one in 25 patients (45.5%), two in 17 (30.9%),

**Table 1** Baseline characteristics of patients according to TCCS findings

Characteristics	Total n = 143	ICAS ≥ 50%		p-value*
		No = 88 (61.5%)	Yes = 55 (38.5%)	
Age, median ± SD*	63.57 ± 11.13	63.15 ± 11.14	64.25 ± 11.18	0.46
Male sex (%)	89 (62.2)	50 (56.8)	39 (70.9)	0.09
<b>Ethnicity<sup>#</sup></b>				
White	90 (62.9)	52 (59.1)	38 (69.1)	0.44
<b>Risk Factors</b>				
Hypertension (%)	110 (76.9)	68 (77.3)	42 (76.4)	0.90
Diabetes (%)	58 (40.6)	38 (43.2)	20 (36.4)	0.41
Current smoker (%)	47 (32.9)	29 (32.9)	18 (32.7)	0.97
Prior stroke or TIA (%)	63 (44.1)	39 (44.3)	24 (43.6)	0.93
Cardiomyopathy (%)	32 (22.4)	19 (21.6)	13 (23.6)	0.77
Atrial fibrillation (%)	27 (18.9)	21 (23.9)	10 (18.2)	0.42
Chagas disease (%)	13 (9.1)	10 (11.4)	3 (5.5)	0.23
Dyslipidemia (%)	56 (39.2)	37 (42.1)	19 (34.5)	0.37
Alcoholism	45 (31.5)	24 (27.3)	21 (38.2)	0.17
Prior aspirin use (%)	59 (41.3)	33 (37.5)	26 (47.3)	0.24
Prior statins use in dyslipidemia (%)	24 (16.8)	15 (17.0)	9 (16.4)	0.62
NIHSS, median (IQR)*	7 (3–15)	6 (3–13)	10 (4–19)	0.004
Glasgow, median (IQR)*	15 (12–15)	15 (13.5–15)	14 (11–15)	0.08
<b>Event type</b>				
AIS (%)	124 (86.7)	77 (87.5)	47 (85.5)	
TIA (%)	19 (13.3)	11 (12.5)	8 (14.5)	0.55
Non-lacunar <sup>#</sup>	105 (74.5)	61 (70.1)	44 (81.5)	0.13
BMI median (IQR)*	26.7 (23.9–30.5)	26.4 (23.4–29.5)	27.1 (24.5–31.2)	0.27
Baseline systolic BP, median (IQR)*	150 (132–164)	140 (130–155)	160 (145–170)	< 0.001
Baseline diastolic BP, median (IQR)*	90 (70.5–93.5)	90 (77.5–91.0)	90 (80–95)	0.29
NIHSS 90 days, median (IQR) <sup>#</sup>	3 (0–6)	3 (0–5)	3 (0–8)	0.87
mRS 90 days ≥ 3 (%) <sup>#</sup>	59 (47.2)	35 (45.5)	24 (50.0)	0.62
Mortality < 3 months (%) <sup>#</sup>	14 (11.2)	6 (7.8)	8 (16.7)	0.57
<b>TOAST</b>				
Undetermined	40 (27.9)	34 (38.6)	6 (10.9)	
Cardioembolism	41 (28.7)	27 (30.7)	14 (25.5)	
Large artery atherosclerosis	41 (28.7)	13 (14.7)	28 (50.9)	< 0.0001
Small artery occlusion	17 (11.9)	11 (12.5)	6 (10.9)	
Other determined causes	4 (2.8)	3 (3.4)	1 (1.8)	

Abbreviations: AIS, acute ischemic stroke; BMI, body mass index; BP, blood pressure; GCS, Glasgow Coma Scale; IQR, interquartile range; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment. Notes: \*Data expressed as median and interquartile range; # missing data were removed from the analysis.

**Table 2** Laboratorial baseline characteristics of patients according to TCCS findings

Characteristics; N (IQR)	Total N = 143	ICAS $\geq$ 50%		p-value
		No = 88 (61.5%)	Yes = 55 (38.5%)	
HbA1C (%)	6.2 (5.6–7.5)	6.1 (5.6–7.2)	6.4 (5.6–8)	0.30
HbA1C $\geq$ 6.5 (%)*	40 (44.9)	24 (42.8)	16 (48.5)	0.60
Hemoglobin (g/dL)	14.2 (12.8–15.3)	14.1 (12.9–15.5)	14.4 (12.6–15.1)	0.95
Hematocrit (%)	43 (39–46)	42 (39–46)	43 (38–45)	0.66
Total cholesterol (mg/dL)	173 (144–208)	176 (45–206)	173 (138–208)	0.54
LDL cholesterol (mg/dL)	110 (83–144)	111 (84–144)	102 (83–136)	0.46
HDL cholesterol (mg/dL)	35 (30–43)	36 (30–45)	32 (27–39)	0.02
Triglycerides (mg/dL)	120 (87–165)	119.5 (85–159)	127 (100–168)	0.57

Abbreviations: HbA1C, glycosylated hemoglobin; HDL, high-density lipoprotein; ICA, intracranial arterial stenosis; IQR, interquartile range LDL, low-density lipoprotein.

Note: \*values show the number and percentage of patients, missing values were excluded.

**Table 3** Association with ICAS in the multivariate analysis

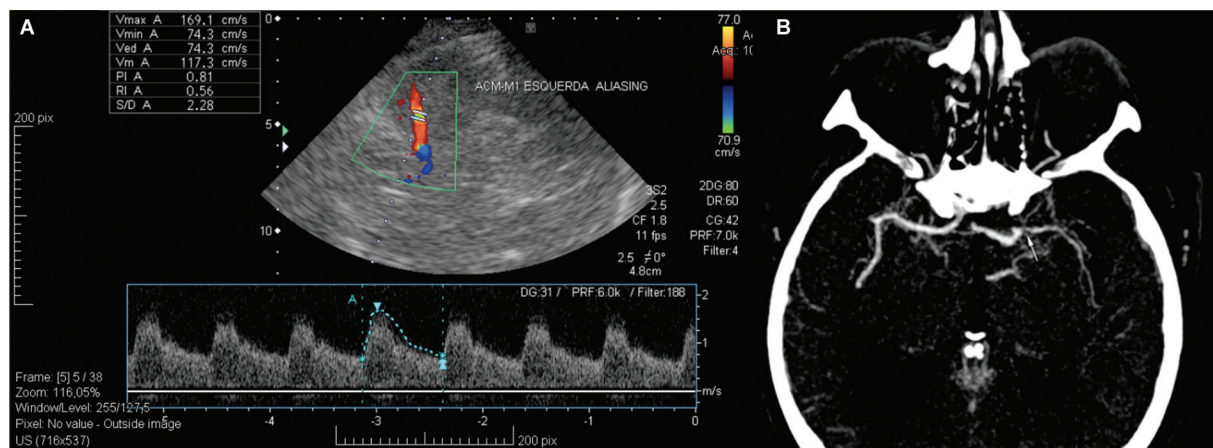
	Stenosis $\geq$ 50%		OR (95% CI)	p-value
	No = 88 (61.5%)	Yes = 55 (38.5%)		
SBP (IQR)	140 (130–155)	160 (145–170)	1.02 (1.01–1.05)	0.008

Abbreviations: CI, confidence interval; ICAS, intracranial arterial stenosis; IQR, interquartile range; OR, odds ratio adjusted; SBP, systolic blood pressure. Note: The variables considered in the model are male sex, NIHSS, Glasgow, systolic blood pressure, and HDL cholesterol.

**Table 4** Site of ICAS  $\geq$  50%

Location	$\geq$ 50% (N = 54)	Subocclusion/occlusion (N = 56)	Total
Right – TICA	7	2	9 (8.2%)
Right – M1CA	6	8	14 (12.7%)
Right – M2CA	0	5	5 (4.5%)
Right – ACA	4	1	5 (4.5%)
Right – P1CA	7	2	9 (8.2%)
Right – P2CA	2	1	3 (2.7%)
Right – VA	0	9	9 (8.2%)
BA	2	7	9 (8.2%)
Left – TICA	3	1	4 (3.6%)
Left – M1MCA	9	8	17 (15.5%)
Left – M2MCA	3	2	5 (4.5%)
Left – ACA	1	1	2 (1.8%)
Left – P1CA	5	1	6 (5.5%)
Left – P2CA	4	1	5 (4.5%)
Left – VA	1	7	8 (7.3%)

Abbreviations: ACA, anterior cerebral artery; BA, basilar artery; ICAS, intracranial arterial stenosis; M1CA, M1 segment of the middle cerebral artery; M2CA, M2 segment of the middle cerebral artery; P1CA, P1 segment of the posterior cerebral artery; P2CA, P2 segment of the posterior cerebral artery; TICA, terminal internal carotid artery; VA, vertebral artery.



**Figure 1** (A) Intracranial stenosis in the M1 segment of the left middle cerebral artery detected by TCCS (mean flow velocity of 169.1 cm/s). (B) Confirmation by computed tomography angiography (white arrow).

three in 5 (9.1%), four in 6 (10.9%), and five in 2 patients (3.6%). Overall, ICAS was most commonly located in the anterior circulation ( $n=61$ , 55.5%), especially in the left M1 segment (15.5%) and in the right M1 segment (12.7%).

The TCCS showed a good performance in predicting ICAS compared with CTA (Cohen kappa: 0.58; area under the curve [AUC]: 0.88; 95% CI 0.69–0.92;  $p < 0.0001$ ) with 74% of sensitivity, 87% of specificity, 65% of predictive positive value, and 90% of predictive negative value (► **Figure 1** and ► **Table 5**).

## DISCUSSION

This study performed at a public tertiary academic stroke center in Brazil found a high frequency (38.5%) of ICAS compared with other Western studies, which indicated 8 to 10% of occurrence.<sup>18,19</sup> To the best of our knowledge, no previous study evaluating the frequency and severity of ICAS assessed by TCCS has been provided in Brazil, and limited studies have investigated the prevalence of this condition in Brazilian patients by other methods. Despite 15.9% of inadequate transtemporal echo-window, we were able to show

**Table 5** Performance of TCCS compared with CTA in MCA  $\geq$  50% of 100 patients

	MCA	95%CI
AUC	0.88	0.69–0.92
Sensitivity	0.74	0.53–0.87
Specificity	0.87	0.76–0.93
PPV	0.65	0.49–0.78
NPV	0.90	0.83–0.95
LR+	5.58	2.9–7.75
LR-	0.30	0.15–0.60

Abbreviations: AUC, area under the curve; CI, confidence interval; CTA, computed tomographic angiography; LR+, positive likelihood ratio; LR-, negative likelihood ratio; MCA, middle cerebral artery; NPV, negative predictive value; PPV, positive predictive value; TCCS, transcranial color-coded duplex sonography.

high rates of ICAS with consecutive enrollment of acute stroke patients evaluated by the same methodology. We believe that one of the reasons for the high rates found in our study may be the systematic investigation of the intracranial vasculature.

It is important to mention that none of our patients met clinical and/or radiological suspicion criteria for vasculitis, inflammatory arteriopathies, intracranial dissection, or reversible cerebral vasoconstriction syndrome. We also excluded from the sample patients who presented clinical and laboratory criteria for anemia, which allows us to assume that the sample analyzed possibly corresponds to the intracranial atherosclerotic disease.

Stroke is a heterogeneous disease, and intracranial atherosclerosis is considered one of the most common causes of AIS worldwide.<sup>20,21</sup> Its incidence and prevalence vary between geographical regions and ethnicities, even in Asian countries, where it accounts for about 50% of cases.<sup>22,23</sup> In Western countries, ICAS has historically been poorly studied and may be underestimated compared to extracranial lesions.<sup>18,24,25</sup> In 1995, Sacco et al. found 8% of intracranial atherosclerosis in a stroke population of 438 patients (35% Black, 46% Hispanic, and 19% White). The rate of extracranial atherosclerosis was similar between ethnic groups; however, intracranial lesions were more frequent in Blacks and Hispanics (OR: 7.8; 95% CI: 1.04–57.7).<sup>19</sup> In the present study, there wasn't a significant difference between ethnic groups ( $p=0.44$ ). However, 69.1% of our patients with ICA were White.

Another reason for the high rates of intracranial atherosclerosis is the poor control of classic risk factors for cerebrovascular diseases found in our sample. Systemic arterial hypertension was the most frequent risk factor in our patients, with a prevalence rate of 76.9%, followed by prior stroke or TIA (44.1%), diabetes (40.6%), and dyslipidemia (39.2%). A study conducted on stroke patients detected that those with MCA stenosis had a higher prevalence of hypertension, hypercholesterolemia, and diabetes.<sup>26</sup> Several other studies have also indicated a correlation between high blood pressure and ICAS.<sup>27–29</sup>

In our study, systolic blood pressure on admission was significantly higher in patients with ICAS ( $p < 0.001$ ) and it was the only independently associated risk factor found in the multivariate analysis. One of the pathophysiological explanations for this might be a preexistent history of systemic arterial hypertension.

This data is consistent with other studies, including stroke-free populations with intracranial atherosclerosis.<sup>30-32</sup> A Chinese study performed between 2009 and 2013 also showed a strong correlation between high blood pressure and symptomatic atherosclerosis of the internal carotid artery (OR: 5.98; 95% CI: 1.79-19.98) and other asymptomatic intracranial atherosclerosis (OR: 2.56; 95% CI: 1.22-5.37).<sup>33</sup>

Of the 56 (39.2%) previously dyslipidemic patients, only 24 (42.8%) were taking statins. The correct use of statins was found in 15 (17.0%) patients without ICAS and in only 9 (16.4%) of those with diagnosis, demonstrating a failure to control one of the most critical risk factors for atherosclerosis and stroke.

Concerning stroke severity, patients with ICAS had higher NIHSS scores ( $p = 0.004$ ) on admission, which may demonstrate a trend to more severe strokes in these circumstances, similar to previous studies.<sup>34</sup> Nevertheless, this data was not statistically significant, nor was associated with functional outcomes and mortality at 3 months. A study conducted by Lau et al. with 39% of ICAS prevalence checked by CTA, the patients had more severe strokes (median NIHSS: 9 vs. 3;  $p < 0.001$ ), worse outcomes at 6 months (mRS: 0-2; 57 vs. 73%;  $p < 0.001$ ), and higher mortality (18 vs. 8%;  $p = 0.001$ ).<sup>35</sup>

Many previous studies reported an association between low levels of HDL and the development of intracranial atherosclerosis.<sup>36</sup> In an analysis of the CICAS study, low HDL levels are strongly associated with the development of ICAS with an inverse relationship between both ( $p = 0.001$ ).<sup>37</sup> In our study, the level of HDL was significantly lower in patients without ICAS than in those with ( $p = 0.02$ ).

Our study has some limitations, mainly because the TCCS is an operator-dependent technique and can sometimes result in incomplete assessments due to unsatisfactory transtemporal bone windows. However, it offers a noninvasive option that can be easily and quickly repeatable at the bedside, allowing accurate evaluation of cerebral blood flow and providing information about anatomical structures.<sup>6,15,38</sup> Furthermore, we performed the study in a single center, and the results were limited to patients with AIS or TIA. Despite previously mentioned limitations, it is essential to note that all selected patients were consecutively evaluated by TCCS, and the characteristics of patients with and without transcranial windows were similar, reducing the possibility of a relevant selection bias. Another possible limitation was that we could not perform CTA on all patients due to contraindications. Nevertheless, our results support the application of TCCS as a diagnostic strategy in Brazilian stroke centers, particularly those lacking more modern imaging techniques.

In conclusion, our study shows that ICAS is a common condition in our population, identified in about one third of

patients admitted with AIS or TIA. Most of these ICAS were symptomatic and considered to be culprits for the stroke episodes. Due to the high prevalence of significant ICAS in the Brazilian population, it is believed that inclusion of TCCS is essential as a bedside examination to evaluate stroke etiology, particularly in patients with high blood pressure on admission. These preliminary findings support further collaborative initiatives among stroke physicians to increase ICAS detection in Brazilian patients with AIS or TIA.

#### Authors' Contributions

LJAR: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, visualization, writing – original draft, and writing – review and editing; MCZZ, RSA, MCL: investigation, methodology, writing – review & editing; MRC: conceptualization, formal analysis, methodology, visualization, writing – original draft, and writing – review and editing; CMAB: investigation, methodology, and writing – review and editing; PTCP: conceptualization, methodology, visualization, writing – original draft, and writing – review and editing; SCM: formal analysis, writing – original draft; DGA: methodology, visualization, and writing – review and editing; OMPN: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, visualization, writing – original draft, and writing – review and editing.

#### Conflict of Interest

The authors have no conflict of interest to declare.

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