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ARTICLE

Multidetector computed tomography angiography in clinically suspected hyperacute ischemic stroke in the anterior circulation: an etiological workup in a cohort of Brazilian patients

Angiotomografia computadorizada multidetectores na avaliação da suspeita clínica de acidente vascular encefálico isquêmico hiperagudo da circulação anterior: determinação etiológica precoce em um grupo de pacientes brasileiros

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ABSTRACT

Objective: The potential of computed tomography angiography (CTA) was assessed for early determination of stroke subtypes in a Brazilian cohort of patients with stroke. **Method:** From July 2011 to July 2013, we selected patients with suspected hyperacute stroke (< 6 hours). Intracranial and cervical arteries were scrutinized on CTA and their imaging features were correlated with concurrent subtype of stroke. **Results:** Stroke was documented in 50/106 selected patients (47.2%) based on both clinical grounds and imaging follow-up (stroke group), with statistically significant arterial stenosis and vulnerable plaques on CTA. Intracranial large artery disease was demonstrated in 34% of patients in the stroke group. Partial territorial infarct prevailed (86%) while artery-to-artery embolization was the most common stroke mechanism (52%). **Conclusion:** Multidetector CTA was useful for the etiologic work-up of hyperacute ischemic stroke and facilitated the knowledge about the topographic pattern of brain infarct in accordance with its causative mechanism.

Keywords: tomography, MDCT, stroke, cerebral infarction.

RESUMO

Objetivo: Avaliar o potencial da angiotomografia computadorizada multidetectores (ATCM) na determinação etiológica precoce do acidente vascular encefálico (AVE) e correlacionar o mecanismo causal com o padrão de infarto. **Método:** De Julho de 2011 a Julho de 2013, foram selecionados os pacientes com suspeita clínica de AVE hiperagudo. Os achados da ATCM dos vasos intracranianos e cervicais foram correlacionados com a etiologia final do evento. **Resultados:** AVE foi confirmado em 50/106 pacientes (47,2%). Estes apresentaram alterações angiográficas estatisticamente mais relevantes. Aterosclerose dos grandes vasos intracranianos esteve presente em 34% destes pacientes. O padrão radiológico topográfico de infarto mais comum foi o infarto territorial parcial (86%). A embolização arterio-arterial foi o mecanismo mais prevalente (52%). **Conclusão**: A utilização da ATCM traz benefícios na detecção etiológica precoce dos pacientes com suspeita de AVE hiperagudo, além de possibilitar o entendimento do padrão radiológico topográfico de acordo com o mecanismo causal do evento isquêmico.

Palavras-chave: tomografia, ATCM, acidente vascular encefálico, infarto cerebral.

Accurate classification of ischemic stroke based on etiology is essential for research because stroke outcome, recurrent stroke rate, and strategies for secondary stroke prevention differ according to stroke subtype[1,2]. Furthermore, stroke subtype is used to describe patients' characteristics in clinical trials, group patients in epidemiological studies, phenotype patients in genetic studies, and classify patients for therapeutic decision-making in daily practice[2,3,4]. Topographic radiologic patterns of brain infarctions might predict prognosis and correlate well with the underlying pathophysiology and imaging findings[5].

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Early determination of the etiologic factors of ischemic stroke is essential for secondary prevention because the risk of recurrence is highly dependent on the underlying cause[6,7]. Extra- or intra-cranial atheromas, cardioembolic sources, and microvascular disease have been identified as the major causes of ischemic stroke[8,9].

The proportions of patients with different ischemic stroke subtypes have been reported to differ for each race-ethnic group[10,11,12]. While Caucasians have an increased risk for cardioembolic strokes[10], Asian patients with ischemic stroke show increased incidence of intracranial large-artery disease (ILAD)[11], and cervical arterial disease is more often reported in western patients[12]. In the Brazilian population, such differences remain unclear.

Recent advances in computed tomography (CT) technology have improved the feasibility of its use in clinical settings. Multidetector CT angiography (MDCTA) improves the sensitivity and inter-rater reliability of detecting acute stroke[13]. In addition, it is an accurate and powerful noninvasive tool for assessing carotid artery disease in the setting of hyperacute ischemic stroke, including the detection of atherosclerosis involvement in extra- and intra-cranial vessels. However, only a few studies have reported the use of MDCTA to define stroke etiology in our population[14]. To the best of our knowledge, MDCTA has not yet been used to study the etiology of stroke in a Latin American population.

In this study, we assessed the potential of the use of MDCTA for the early detection of the etiology of hyperacute ischemic stroke in the middle cerebral arteries (MCA) in a Brazilian cohort of patients and subsequently correlated the topography and causative mechanisms of infarcts.

METHOD

Patient selection

This study is part of a larger protocol in a single institution of the use of MDCTA techniques to evaluate hyperacute stroke, and the protocol has been reviewed and approved by the Institutional Review Board and the local ethics committee. From July 2011 to July 2013, adult patients (≥ 18 years old) who presented with hyperacute symptoms (< 6h) that were consistent with focal acute ischemia of the MCA and who had undergone CTA were considered eligible. The patient or their guardian signed the informed consent.

Patients with contraindications regarding intravenous iodine contrast administration were excluded from the study. In addition, we excluded patients who refused to participate in the study, patients with examinations with inadequate image quality, and patients who had posterior circulation strokes as their final diagnosis.

Protocol

All examinations were conducted with a previously reported institutional protocol[14] with a minimum dose of ionizing radiation and intravenous iodinated contrast in a Philips Brilliance 64-slice CT scanner (Brilliance CT 64 Channel, Philips Medical, Eindhoven, The Netherlands). The examinations included non-contrast computed tomography and cervical and intracranial MDCTA, which required up to 5 min.

MDCTA was performed after intravenous administration of 50 mL of nonionic iodinated contrast (Ultravist®; 300 mg I/mL) at a rate of 5 mL/s using a dual-head power injector (Bayer HealthCare LLC, Whippany, NJ, USA) with an 18-G intravenous access, which was usually located in the cubital vein. The region of interest was placed in the aortic arch to determine the self-timer of the apparatus. When the attenuation in this region reached 160 HU, acquisition of the sections from the aortic arch to the vertex of the skull was initiated. Source images of CTA (CTA-SI) were postprocessed to obtain maximum intensity projections and three-dimensional views of the intracranial and extracranial arteries.

Analysis

All of the data were postprocessed with commercially available software on a workstation (Extended Brilliance Workspace v3.5.0.2250, Philips Medical Systems B.V., Best, The Netherlands). Two neuroradiologists who were experienced in vascular imaging and were blinded to the outcomes independently analyzed all of the CTA-SI from the emergency room examination and, subsequently, the maximum intensity projections and the three-dimensional reconstructions. All discrepancies were solved by consensus.

All patients were classified as having either normal or abnormal extracranial cervical carotid arteries. Vascular abnormalities that potentially correlated with concurrent stroke were discriminated based on their imaging features.

If a plaque was visible on CTA-SI, it was categorized based on the grade of stenosis and type of plaque. The severity of stenosis was defined as the remaining lumen at the site of stenosis as a percentage of the normal lumen distal to the stenosis and categorized as < 50%, 50%-99%, and 100% (arterial occlusion). The vessel diameters were measured on the plane that was perpendicular to the vessel course. According to the TOAST criteria[7], we considered stenosis to be relevant if the plaque resulted in a vessel diameter reduction of more than 50%.

The plaques' morphologies were assessed subjectively by consensus, and their densities were measured with the region of interest. The plaque composition was analyzed according to the following previously proposed classification[15]: (1) non-calcified plaques (density, ≤ 50 HU), (2) calcified plaques (mean attenuation, > 130 HU), and (3) mixed plaques (mean attenuation varying from 51 to 130 HU). For plaque morphology analysis, its surface was considered regular or irregular. A stable plaque was defined as a plaque that was calcified with a regular surface. If the plaque was non-calcified or mixed and it had an irregular surface with or without ulcerations, it was considered a vulnerable plaque.

The intracranial cerebrovascular system was scrutinized to be interpreted according to current literature[11,16,17]. A diagnosis of atherothrombosis was assumed when relevant cervical artery atherosclerosis was concomitant with a MCA thrombus. However, a cardioembolic origin was determined when a cardiac source was confirmed in the absence of relevant cervical artery disease. A diagnosis of ILAD was adopted when partial or total atherosclerotic MCA obstruction was documented in the absence of relevant cervical artery disease or cardioembolic source. If was detected a non-relevant cervical artery disease combined with partial or total atherosclerotic MCA obstruction was assumed that there was concurrent ILAD and extracranial atherosclerosis. Follow-up images were analyzed in order to confirm ischemic stroke. The topographic radiologic patterns of the brain infarctions visible on non-contrast CT were defined with the OCSP classification[4], which resulted in malignant, large, and limited infarcts for MCA territorial strokes. Limited infarcts were those that covered only 1 of the 3 MCA territories (deep, superficial anterior, or superficial posterior). Large infarcts were defined as those covering at least 2 of these 3 MCA territories. Malignant infarction referred to complete or almost complete MCA infarctions[18].

Finally, using the SSS-TOAST algorithm[8], the patients were classified according to the results of their individual examinations that included cervical Doppler ultrasonography, cardiac echo, and electrocardiogram; this was termed the final classification.

Statistical analysis

All of the information was entered into a database with Excel 2011 (Version 14.0.0; Microsoft Corporation, Redmond, WA, USA). We then entered all of the data into IBM SPSS Statistics software (Version 20.0 for Mac; IBM Corporation, Armonk, NY, USA). X^2 tests were used to compare the variables between patients with and without brain infarctions and within the group of patients with brain infarctions. P-values less than 0.05 were considered statistically significant.

RESULTS

A total of 134 patients were recruited for this study. According to the previously reported criteria, 106 patients were selected for the retrospective analysis. They were divided according to their outcomes. An anterior circulation stroke was documented in 50/106 patients (47.2%) based on both clinical and imaging follow-up findings (stroke group), while 56/106 patients (52.8%) showed no evidence of brain ischemia (non-stroke group).

Unremarkable results on the cervical MDCTA were documented in 18 patients (18/50, 36.0%) patients in the stroke group. In the remaining patients, non-relevant stenosis was found in 17 patients (17/50, 34.0%) patients, while relevant stenosis in the cervical arteries was found in 15 patients (15/50, 30.0%) (Figure 1), including 5 patients (5/50, 10.0%) with stenosis diameters > 50%, 4 patients (4/50, 8.0%) with occlusive disease and the remaining 6 patients (6/50, 12.0%) with cervical arterial dissections.

Conversely, relevant stenosis was only seen in 4 patients from the non-stroke group (4/56, 7.0%), while 20 patients (20/56, 36.0%) in this group had normal results on MDCTA. The remaining 32 (32/56, 57.0%) had only non-relevant stenosis (X^2 test: $p = 0.01$; Table 1).

Although plaques may not cause relevant obstruction, they might be responsible for cerebral infarctions according to their characteristics. When patients with non-relevant stenosis were examined, 10 patients (10/17, 59.0%) in the stroke group were found to have vulnerable plaques. In contrast, 10 patients in the non-stroke group (10/32, 31.0%) were diagnosed with vulnerable plaques. (X^2 test: $p = 0.01$; Table 1).

Of the 50 patients included in the stroke group, 7 (7/50, 14.0%) had normal intracranial and extracranial vessels. Imaging findings that were compatible with ILAD (Figure 2) were documented in 7 patients (7/50, 14.0%), while 12 (12/50, 24.0%) had only cervical carotid atherosclerosis and 10 (10/50, 20.0%) had concurrent ILAD and extracranial atherosclerosis. The remaining 14 patients (14/50, 28.0%) had atherothrombosis

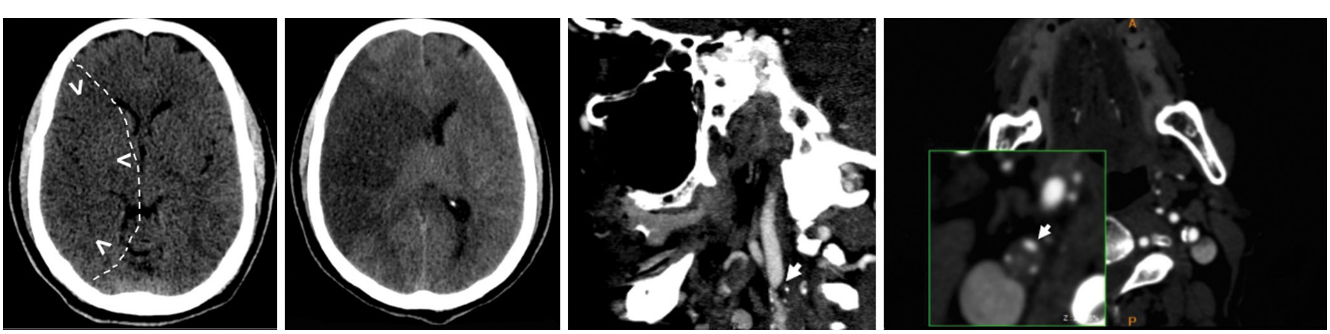

Figure 1. A 56-year-old man presented within 60 minutes of a left hemiplegia. (A) Initial non-contrast CT with subtle hypoattenuating area in the MCA territory (arrowheads). Dotted line demonstrated a more extensive ischemic area according to the follow-up exam; (B) Follow-up imaging after 3 days demonstrated hypoattenuation in almost complete right MCA territory, which was compatible with brain ischemia as a result of artery-to-artery embolism; (C) Sagittal CTA MIP image demonstrated a heterogeneous plaque (arrow) determining severe luminal obstruction (90%); and (D) Axial imaging confirming the severe obstruction determined by heterogeneous plaque.

Table 1. Extracranial atherosclerosis in both Groups (stroke and non-stroke).

Relevant Stenosis	Total (%) (n = 106)	Stroke Group (%) (n = 50)	Non-stroke Group (%) (n = 56)	p
Present	19	15 (30)	4 (7)	0.01*
Absent	87	35 (70)	52 (93)	0.14
Type of plaque	**Total (%) (n = 49)**	**Stroke Group (%) (n = 17)**	**Non-stroke Group (%) (n = 32)**	**p**
Vunerable	20	10 (59)	10 (31)	0.01*
Stable	29	7 (41)	22 (69)	0.21

*p < 0.05.

Figure 2. An 80-year-old woman presented within 120 minutes of onset of left hemiplegia caused by ILAD. (A) Axial CTA MIP image demonstrated at least 50% stenosis in the right MCA. Dotted line demonstrated a more extensive ischemic area according to the follow-up exam; (B) Tridimensional (3D) view of the extracranial right carotid arteries only demonstrated parietal irregularities that corresponds a smalls calcified non-stenotic plaques; (C) Noncontrast CT demonstrated subtle effacement of the right insula (arrowheads). The dotted line demonstrated a more extensive ischemic area according to the follow-up exam; and (D) Imaging follow-up after 3 days demonstrated a large ischemic stroke in the MCA territory.

or cardioemboli with thrombi in the intracranial system. Of the 56 patients included in the non-stroke group, only 2 (2/56, 3.5%) had concurrent intra- and extra-cranial atherosclerosis, none had only intracranial disease, and 34 (34/56, 60.8%) had isolated extracranial disease (32 irrelevant stenosis and 2 relevant stenosis). Twenty patients (20/56, 35.7%) had unremarkable CTAs (X^2 test: p = 0.01; Table 2).

Based on the final classification using the SSS-TOAST algorithm, our patients were divided as: 25 (25/50, 50.0%) with large artery disease, 10 (10/50, 20.0%) with cardioemboli (Figure 3), 5 (5/50, 10.0%) with undetermined causes, 3 (3/50, 6.0%) with small-artery disease, 3 (3/50, 6.0%) with more than one evident mechanism, and 4 (4/50, 8.0%) with other causes (all of them cervical artery dissection) (Figure 4).

After reviewing the follow-up imaging, we classified the patients in the stroke group based on topographic radiologic patterns of brain infarction (OCSP classification). Forty-three (43/50, 86.0%) had territorial infarcts, of which 27 had limited, 7 had large, and 9 had malignant territorial infarcts; 3 (3/50, 6.0%) had centrum oval infarcts; 3 (3/50, 6.0%) had lacunar infarcts, and 1 (1/50, 2.0%) had a watershed infarct (Figure 5). When we analyzed the centrum oval infarcts, we found that all of them (3/3, 100.0%) were related to large artery atherosclerosis, while the lacunar infarcts (3/3, 100.0%) were due to small-artery occlusion. The only watershed infarct (1/1, 100.0%) was caused by cervical arterial dissection.

By correlating the OCSP and SSS-TOAST classifications we observed that cervical carotid atherosclerosis caused large or malignant brain infarctions in 6 patients (6/25, 24.0%), including 5 patients (5/6, 83.3%) with concurrent ILAD and extracranial disease. Large or malignant infarctions were also diagnosed in 6 patients with cardioemboli etiology (6/10, 60.0%) and in 2 patients with cervical arterial dissections (2/4, 50.0%).

DISCUSSION

Extracranial carotid atherosclerotic disease has been reported as the major risk factor for stroke, and the main mechanism is related to artery-to-artery embolization from either an atherosclerotic plaque or an acute occlusion of the carotid artery with distal propagation of the thrombus[19]. Accordingly, cervical carotid atherosclerotic disease was demonstrated

Table 2. Intra and extracranial findings in both Groups (stroke and non-stroke).

	Total (%) (n = 106)	Stroke Group (%) (n = 50)	Non-stroke Group (%) (n = 56)	p
Normal vessels	24	07 (14.0)	20 (35.8)	0.01*
Atherothrombosis or cardioemboli	14	14 (28.0)	00 (00.0)	0.01*
ILAD	07	07 (14.0)	00 (00.0)	0.01*
Relevant cervical disease	46	09 (18.0)	02 (03.5)	< 0.05*
Irrelevant cervical disease		03 (06.0)	32 (57.2)	0.01*
Extra and intracranial	12	10 (20.0)	02 (03.5)	< 0.05*

ILAD: Intracranial large-artery disease. *$p < 0.05$.

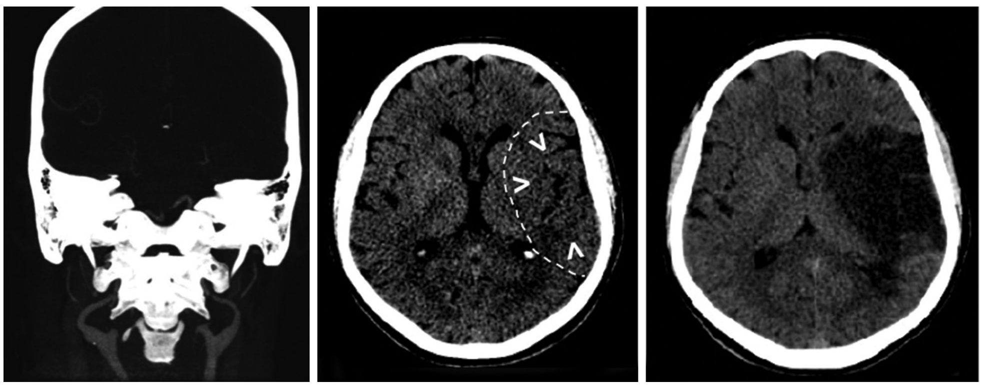

Figure 3. A 66-year-old man presented within 90 minutes of onset of right hemiplegia and aphasia. (A) Coronal CTA MIP image with unremarkable findings of the cervical carotid arteries; (B) Noncontrast CT demonstrates subtle effacement of the left insular cortex (arrowheads). Dotted line demonstrated a more extensive ischemic area according to the follow-up exam; and (C) Imaging follow-up after 2 days confirmed a large infarct in the MCA territory. A cardiac source of emboli was confirmed.

on CTA in the majority of our patients, and it was the main risk factor for stroke with half of them presenting relevant stenosis or vulnerable plaques on cervical arteries.

Luminal narrowing is the standard parameter used for reporting the severity of carotid atherosclerosis[20]. However, plaque morphology also plays an important role as it directly correlates with the risk of embolism and occlusion, thus resulting in cerebral ischemia[21].

Several studies have highlighted that MDCTA findings closely correlate with those from digital angiography for the degree of stenosis, which suggests that the sensitivity of MDCTA in evaluating the degree of stenosis may be comparable to that of angiography but with a lower level of risk[22,23,24,25]. The majority of the patients from our series demonstrated some degree of cervical artery abnormalities that were detected on MDCTA (64.0% in both groups). Our study confirmed that MDCTA was able to detect relevant stenosis on cervical carotid arteries more commonly in patients with brain infarcts (30.0% *versus* 7.0%) whose had the etiology of their ischemic stroke defined in the same moment as the diagnosis of the brain infarction.

Moreover, MDCTA detected vulnerable plaques, even in cases of non-relevant stenosis, in both groups. Although this finding was likely involved in the pathophysiology of the final infarct, further studies are necessary to confirm this. The relevance of the abnormal arteries on MDCTA in defining the stroke mechanism in the stroke group was well supported by our results. The relevance of cervical carotid abnormalities in patients from the non-stroke group (relevant stenosis or vulnerable plaques) remains uncertain as these findings could be related to either transient ischemic attacks or minor infarcts with absent brain lesions or abnormalities not detectable on brain CT.

In patients with non-relevant abnormalities, the percentages of plaques were the same in both groups, but analyzing the characteristics of the plaques on cervical CTA showed that the percentage of the vulnerable plaque type was higher in the stroke group (59.0% *versus* 21.0%), which corroborated data aggregated by Gupta et al. in a meta-analysis that suggested an association of these types of plaques with an increased risk of stroke[26]. Considering these characteristics, our findings corroborated that it is important to examine plaque morphology in addition to the lumen obstruction[11].

Large artery atherosclerosis was the main stroke type in our group of patients, and it involved 50.0% of the cases. Limited infarction was the most common imaging finding. This finding demonstrates a slightly higher prevalence of carotid atherosclerotic disease as a cause for stroke than those previously postulated[2,20,27]. A more precise elucidation of the role of vulnerable plaques in non-relevant stenosis and their implications in the absence of concurrent brain infarcts detectable on CT remains uncertain.

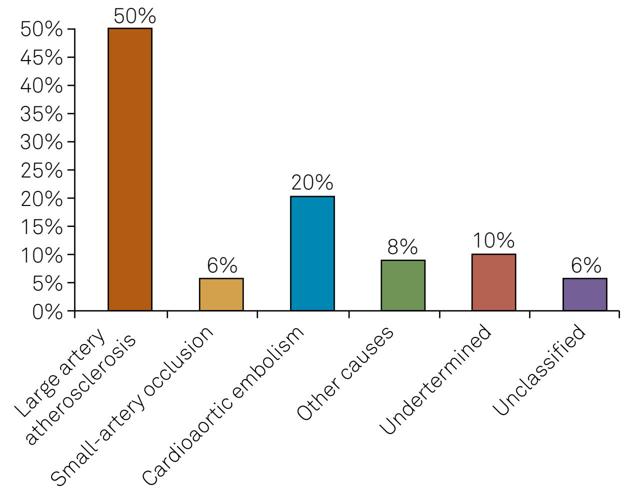

Figure 4. Final classification (SSS-TOAST) of brain infarctions.

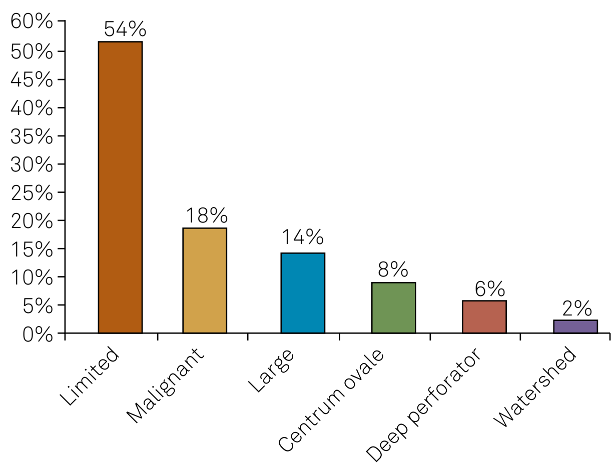

Figure 5. Topographic radiologic pattern of brain infarction.

Atherosclerosis MCA and ICA disease have been associated with racial differences. While MCA disease is often reported in Asians, ICA disease is frequently found in western populations[28]. Man et al.[29] found that 72% of a Chinese cohort of patients had ILAD, which differed from the findings in our patient group, in which 34% had ILAD; 14% had ILAD and 20.0% had ILAD along with cervical arterial disease. Thus, similar to the results from other countries of the western world, our Brazilian patients population more frequently had ICA disease as a well-defined stroke subtype. Despite that, ILAD was largely documented in our series of patients with hyperacute stroke that was isolated or in association with extracranial atherosclerosis, which suggested a relationship between the severity of atherosclerosis in Brazilian patients and the causative factor of clinical stroke. In a majority of our cases, ILAD caused a limited infarct that was similar to cervical atherosclerosis. Otherwise, patients who had these concomitant conditions developed a large or malignant infarct more frequently, which conflicted with the data reported by Man et al.[21].

Considering the OCSP classifications in our subgroup of patients, territorial infarcts prevailed (86.0%). Of these, 32.0% were large or malignant infarcts, which exhibited a higher frequency of clinical deterioration, a minimum chance of better outcome, and a high mortality rate. In patients with large infarcts, the frequency of cardioembolic disease was clearly higher than in those with small brain lesions. Hypothetically, because cardioembolic thrombi tend to be larger, they might stop proximally in the intracranial circulation.

This study's strengths include the use of a new CT technique that is safe and minimally invasive and that is able to evaluate stroke mechanisms and vascular etiology. This protocol is reproducible because MDCTA is widely available and often applicable in hyperacute settings in emergency rooms.

This study had several limitations, including a small sample size, experience based on a single institution, restriction to MCA infarcts, and absence of clinical information. The use of CT for follow-up imaging in our patients might limit the detection of brain lesions, particularly transient ischemic attacks or minor infarcts, and the extension of brain infarcts, which is useful for defining their topography and subtypes. CT has been used in similar reports that have evaluated intracranial and cervical stenosis in hyperacute brain infarcts[11,30]. Although the use of diffusion-weighted imaging has been advocated to be more accurate in detecting brain ischemia and exploring stroke mechanisms, this technique is not included as part of the routine workup in patients with hyperacute stroke[12,29,31]. Brain CT is preferred in our institutional protocol for evaluating hyperacute brain ischemia in the anterior intracranial circulation.

Despite these limitations, this study provided unique data on the relationship between infarct patterns on brain imaging and the likely mechanisms of stroke in a cohort of Brazilian patients.

In conclusion, MDCTA is useful for the etiologic examination of patients with acute ischemic strokes in order to plan future clinical trials for the prevention and treatment of this disorder in Latin American patients. Our data confirmed that patients with suspected hyperacute brain infarcts in the MCA territory could benefit from having MDCTA added to the imaging protocol as a fast, minimally invasive, widely available, and reliable tool for the early determination of the main etiologic factors.

This study suggested that artery-to artery embolization was the most common stroke mechanism in patients with relevant cervical carotid stenosis. Conversely, the absence of cervical carotid abnormalities favored the cardioembolic mechanism with larger brain infarcts. ILAD seems to be a common etiology for stroke, and it correlated with the severity of atherosclerosis in this series of Brazilian patients.

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