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ORIGINAL RESEARCH ARTICLE

Analysis of encephalic lesions on magnetic resonance imaging in patients with Transcranial Doppler high intensity transient signals

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ABSTRACT

Objective: To describe magnetic resonance imaging (MRI) findings of the brain in patients younger than 65 years who were studied by transcranial Doppler (TCD) with microbubble contrast, with a history of cryptogenic cerebrovascular accident (CVA) and suspected patent foramen ovale (PFO).

Materials and methods: This retrospective cross-sectional study included patients of both sexes, younger than 65 years of age.

Results: Our sample (n = 47.47% male and 53% female, mean age is 42 years) presented high-intensity transient signals (HITS) positive in 61.7% and HITS-negative in 38.3%. In HITS-positive patients, lesions at the level of the subcortical U-brains, single or multiple with bilaterally symmetrical distribution, predominated. In patients with moderate HITS, lesions in the vascular territory of the posterior circulation predominated.

Conclusion: In patients younger than 65 years with cryptogenic stroke and subcortical, single or multiple U-shaped lesions with bilateral and symmetrical distribution, a PFO should be considered as a possible cause of these lesions.

Keywords: Transcranial Doppler Ultrasonography; Magnetic Resonance Imaging; Patent Foramen Ovale

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1. Introduction

According to data from the American Heart Association (AHA), the prevalence of stroke in patients between 20 and 59 years of age is up to 2.4% of the population (higher prevalence in women between 40 and 59 years of age)[1,2]. In Argentina, in a study conducted in the city of Junín, a prevalence of 868.1 cases per 100,000 inhabitants was detected (world population-adjusted rate: 473.4 per 100,000 inhabitants), with 79.6% ischemic and 20.4% hemorrhagic events[3]. Multiple predisposing risk factors (RF) for the development of ischemic stroke have been reported[4,5]. In terms of etiology, five categories are recognized according to the Trial of ORG 10,172 in Acute Stroke Treatment (TOAST) (TOAST: atherosclerosis, cardioembolic, small vessel disease, other determined etiology, and undetermined etiology.)[6]. In young patients with ischemic stroke, those of cryptogenic type ("of undetermined etiology" in its original description) reach up to 30% and 40% in most registries and databases[7-13].

Multiple studies show an association between patent foramen ovale (PFO) and cryptogenic stroke in patients of all ages, especially in those younger than 65 years[14-20]. However, there is little evidence as to which magnetic resonance imaging (MRI) findings of the brain are most frequently associated with stroke from paradoxical embolisms with positive high-intensity transient signals (HITS).

The proposed imaging modalities include: 1) magnetic resonance imaging (MRI) of the brain, 2) transcranial Doppler (TCD) with microbubble contrast, to detect HITS, which are generated from extracranial paradoxical embolisms[21,22].

2. Target

To describe the findings in brain MRI in patients younger than 65 years who were studied by TCD with microbubble contrast, with a history of stroke and suspected PFO.

3. Materials and methods

The present retrospective study included patients of both sexes, under 65 years of age, who were studied by MRI and microbubble contrast-enhanced TCD for clinical suspicion of paradoxical embolism, with a history of stroke and/or PFO, taking into account their risk factors (RF).

3.1 Study protocols

RF: Obtained by a neurologist and added to the clinical history of each patient, following the criteria established by the AHA[2].

DTC: Performed on a single occasion, each study was carried out entirely by a radiologist with experience in the technique, with the assistance and clinical control by a neurologist, also with experience in the technique. A Philips® HD11XE ultrasound scanner with a high-resolution S4-2 sectorial transducer (frequency range 4 to 2 MHz) was used, following the Teague and Sharma technique[23]. Prior to the procedure, the patient was assessed for adequate performance of the Valsalva maneuver, which was evidenced as a decrease in flow velocities and heart rate in the wave spectrum of intracranial arterial flow. Subsequently, a microbubble suspension (**Figure 1**) was formed by mixing 0.2 ml of air, 0.5 ml of the patient's blood, and 5 ml of physiological solution in two 10 ml syringes connected by a three-way stopcock, with the latter to the patient's antecubital vein.

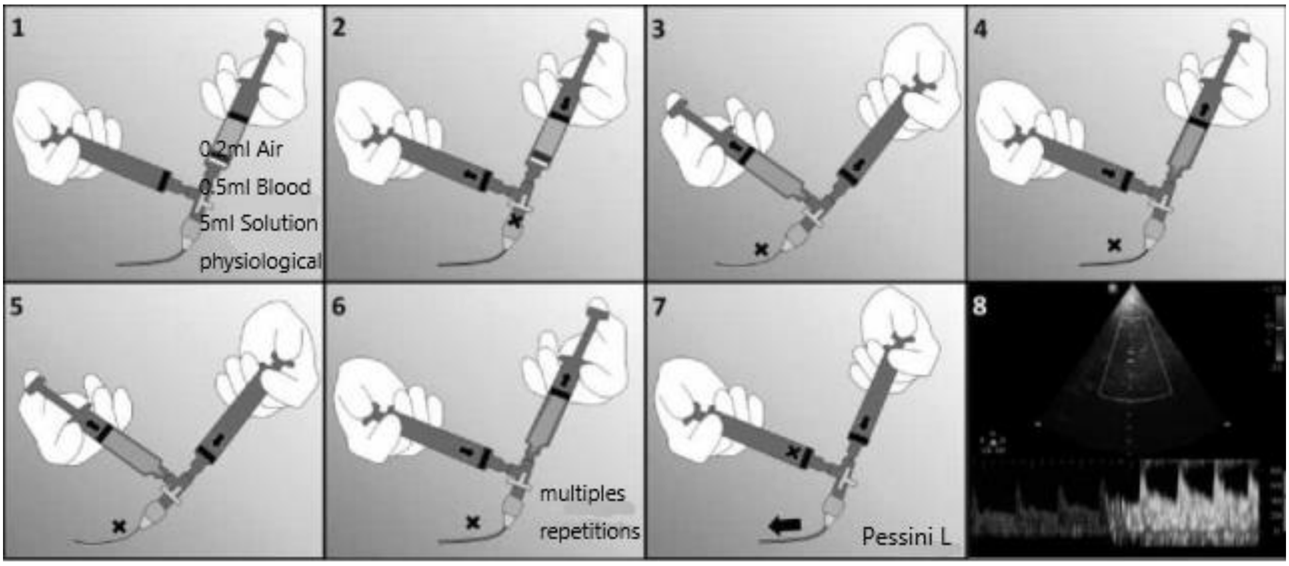

Figure 1. Representative scheme of the steps to be followed to form the microbubble suspension: 1 to 8 in chronological order. Step 1: Aspiration of blood through a peripheral route, towards the syringe with Air and Physiological Solution. Steps 2 to 6: Mixing of the different solutions with production of microbubbles. Step 7: Peripheral injection. Step 8: Positive registration of HITS in the spectrum.

That suspension was immediately injected as a bolus and in conjunction with Valsalva maneuvers for the detection of HITS by TCD at the level of the intracranial circulation, exploring via temporal route the middle cerebral, carotid bifurcation, anterior cerebral and posterior cerebral arteries; and via occipital window the vertebral arteries (segment V4) and the basilar artery (**Figure 2**). In doubtful cases, the same procedure was repeated. The Doppler wave spectrum was obtained continuously at the time of contrast medium injection.

Figure 2. Representative diagram of the disposition of the patient and the physicians (radiologist and neurologist) at the time of the examination.

MRI: Philips® Intera 1.5-T and Siemens® Magnetom Essenza 1.5-T Magnetic Resonators with Sense head coil were used. Images were obtained using Fast Spin Echo (FSE) T2 and *Fluid-attenuated inversion recovery* (FLAIR), Gradient Echo (GRE) T2, Diffusion (DWI) and *Apparent Diffusion* Coefficient (ADC) and Spin Echo (SE) weighted sequences in T1 with 5 mm thick slices. Angio-MRI 3D *Time of Flight* (TOF) examination of intracranial vessels with *Maximum Intensity Projection* (MIP) reconstructions was included.

3.2 Criteria definition

RF: As traditional RF, we consider: arterial hypertension, diabetes, smoking, dyslipidemia, atrial fibrillation-type arrhythmias and ischemic heart disease. As non-traditional RF: hyperhomocysteinemia, use of oral contraceptives and antiphospholipid syndrome are considered.

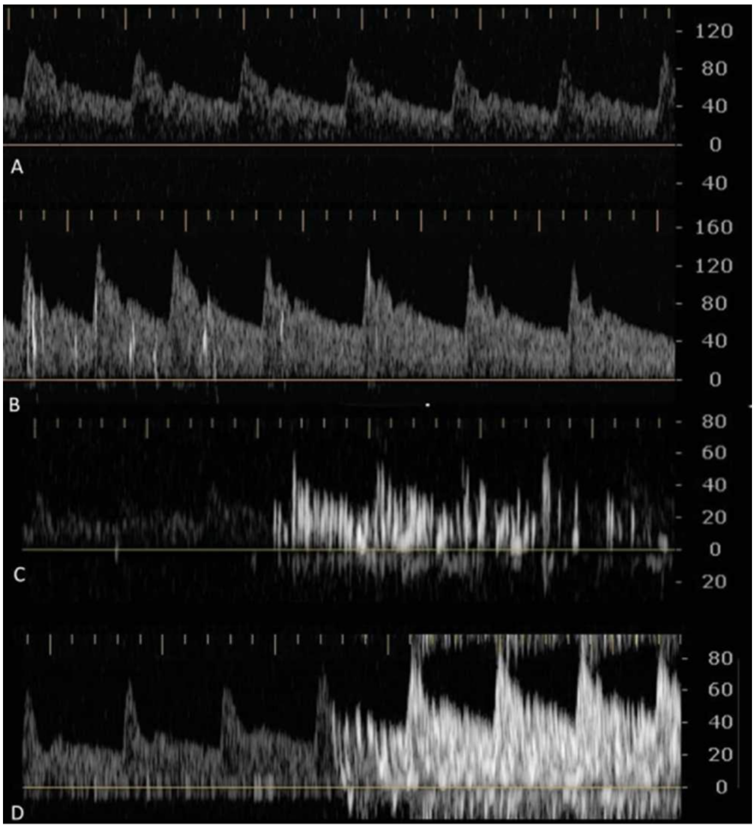

Figure 3. HITS classes detected by transcranial Doppler: **A**: C0, no HITS. **B**: C1, less than 10 HITS. **C**: C2, between 10 and 25 HITS without curtain. **D**: C3, HITS in curtain.

DTC: To be considered as HITS, the detected signals had to meet the following criteria: be transient (less than 300 milliseconds in duration), be of high intensity (three decibels above the background circulation), have a unidirectional signal in the flow velocity spectrum and coincide with a characteristic snapping sound[24]. To define its degree, Blersch's criteria were used[22], recognizing four possible categories: (1)C0: No HITS. (2) C1: less than 10 HITS. (3) C2: between 10 and 25 HITS without curtain. (4)

C3: HITS in curtain (**Figure 3**).

RM: Lesions were defined as those foci hyperintense with respect to the white matter signal in FLAIR sequences, and they were studied taking into account (**Table 1**) their location, distribution (number and symmetry of lesions) and the vascular territory affected.

Table 1. Abbreviations used in this study for location, distribution and vascular territory of lesions.

Location
Supratentorial (ST)
Gray substance (GS)
Nucleus Base (NB)
Subcortical U-fibers (SC)
Periventricular (PV)
Radiated crown (RC)
Corpus callosum (CC)
Infratentorial (IT)
Trunk region (TR)
Cerebellum region (CR)
Distribution
No lesions (NL)
Single lesion (SL)
Multiple unilateral (MU)
Multiple bilaterals (MB)
Vascular territory
Anterior circulation (AC)
Anterior cerebral artery (ACA)
Middle cerebral artery (MCA)
Subsequent circulation (PC)
Trunk arteries (TA)
Cerebellar arteries (CA)
Both, CA and CP (A)

In terms of lesion location, lesions of cortical gray substance (GS), nucleus base (NB), subcortical U-fibers (SC), periventricular level (PV), corona radiata and semioval center (CR) and corpus callosum (CC) were considered at the supratentorial level (ST), and lesions in the brainstem trunk region (TR) and cerebellum region (CR) were considered at the infratentorial level (IT).

Regarding the distribution, patients with no lesions (NI), single lesion (SL), multiple unilateral lesions (MU) and multiple bilateral lesions (MB) were considered as categories.

Regarding vascular territories, the anterior circulation (AC) was studied: the anterior cerebral artery (ACA) and the middle cerebral artery (MCA). In the posterior circulation (PC): the trunk arterie (TA) and the arteries of the cerebellum (AC) was studied.

3.3 Statistical analysis

For the statistical analysis, Fisher's exact test with bilateral p-values was used, with values less than 0.05 being considered statistically significant. To define whether or not the type of lesions is related to pre-existing RF (for example, arterial hypertension or diabetes), Fisher's exact test was also used with calculation of bilateral p.

3.4 Ethical aspects

The present study was approved by the Ethics Committee of the institution where it was performed. The anonymity of all the patients included has been maintained. The authors declare that they have no conflicts of interest related to the present study.

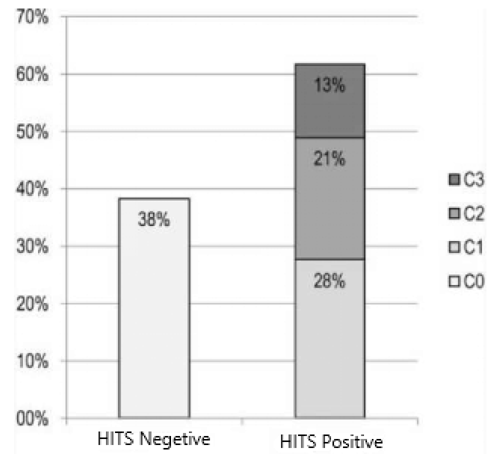

Figure 4. Results of the sample. according to the presence or absence of HITS. and its class. C0: No HITS. C1: less than 10 HITS. C2: between 10 and 25 HITS without curtain. C3: HITS in curtain.

4. Results

A sample (n) of 47 patients under 65 years of age (mean: 42, range: 17–54, SD ± 12.4), who were studied with MRI and TCD with microbubble injection, for suspected stroke (47% male and 53% female), was obtained. Of the patients studied (**Table 2**, **Figure 4**), 61.7% were HITS-positive on TCD (27.6% were C1, 21.3% C2and 12.8% C3), and 38.3% HITS-negative (C0).

4.1 Lesion location

Taking into account that coexistence of lesions in more than one location is possible, we note that (**Table 2** and **Figure 5**):

Of the total number of patients, 78.7% had supratentorial (ST) level involvement, of which 63.2% were HITS-positive and 36.8% HITS-negative.

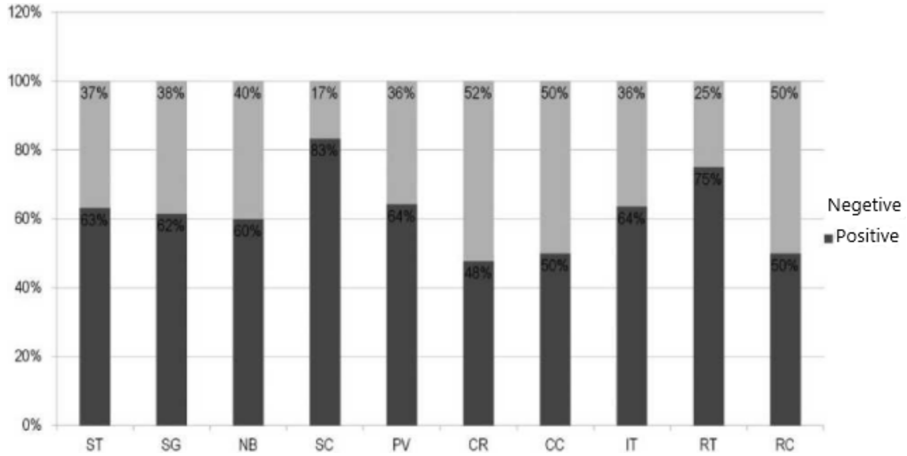

Figure 5. Lesion location. according to positive or negative HITS results. ST: supratentorial. SG: cortical gray matter. NB: nucleus base. SC: subcortical U-fibers. PV: periventricular. CR: corona radiata and semioval center. CC: corpus callosum. IT: infratentorial. TR: trunk region. CR: cerebellar region.

Table 2. Location, distribution and vascular territory affected by lesions in both HITS-positive and HITS-negative patients

Location	**Injuries total (%)**	**HITS (%)**		***p*-value**
		Positive	**Negative**	
ST	78.7	63.2	36.8	0.7155
SG	19.1	61.5	38.5	
NB	14.9	60.0	40.0	
SC	72.3	83.3	16.7	0.0294
PV	19.1	64.3	35.7	
CR	31.9	47.8	52.2	0.0753
CC	2.1	50.0	50.0	
IT	19.1	63.6	36.4	
TR	14.9	75.0	25.0	
RC	4.3	50.0	50.0	0.6918
Distribution				
NL	8.5	75.0	25.0	
SL	38.3	66.7	33.3	0.7590
MU	14.9	42.9	57.1	0.4029
MB	38.3	61.1	38.9	
Vascular territory				
CA	68.1	53.1	46.9	0.1109
ACA	36.2	52.9	47.1	0.3710
ACM	68.1	53.1	46.9	0.1109
CP	44.7	61.9	38.1	
AT	29.8	64.3	35.7	
AC	19.1	55.6	44.4	0.7155
A	21.3	40.0	60.0	0.1500

Abbreviations: A. both (CA and CP); CA. cerebellar arteries; ACA. anterior cerebral artery; MCA. middle cerebral artery; MCA. middle cerebral artery; TA. trunk arteries; CA. anterior circulation; CC. corpus callosum; PC. posterior circulation; CR. corona radiata and semioval center; IT. infratentorial; SL. single lesion; MB. multiple bilateral lesions; MU. multiple unilateral lesions; NB. nucleus base; PV. periventricular; CR. cerebellar region; TR. trunk region; SC. subcortical U-fibers; SG. cortical gray matter; NL. no lesions; ST. supratentorial.

Considering as 100% the total number of patients with lesions in each location, they presented HITS-positive in DTC: 61.5% of patients with lesions in SG, 60% of NB (**Figure 6**), 83.3% of SC (**Figure 7**), 64.3% of PV, 47.8% of CR and 50% of CC. The remaining percentage for each location corresponds to HITS-negative patients.

A total of 19.1% of patients had infratentorial (IT) involvement, of which 63.6% were HITS-positive and 36.4% HITS-negative.

Considering as 100% the total number of patients with lesions in each location, 75% of all patients with lesions in RT and 50% of those with lesions in CR presented HITS-positive in the DTC. The remaining percentage for each location corresponds to patients with HITS-negative lesions.

We highlight that there was a significant relationship between HITS-positive patients and those with lesions at the CS level (p 0.0294).

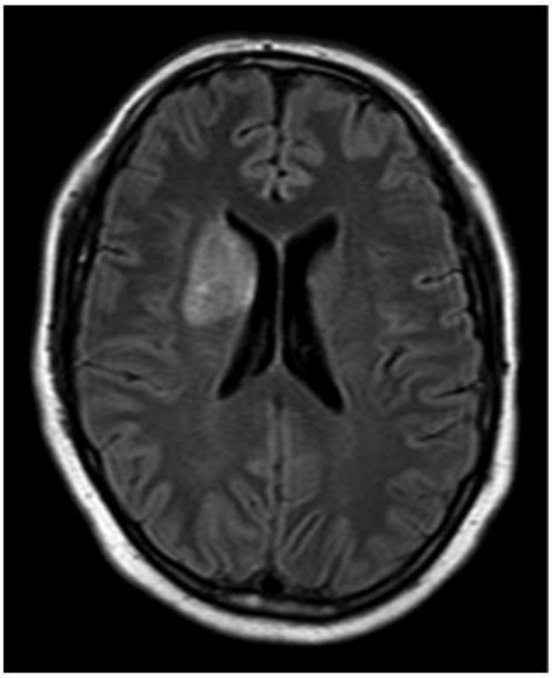

Figure 6. T2 FLAIR image in axial plane showing a lesion affecting the nucleus base (NB). as well as the white matter of the Corona radiata and Semioval Center (CR) of the right cerebral hemisphere.

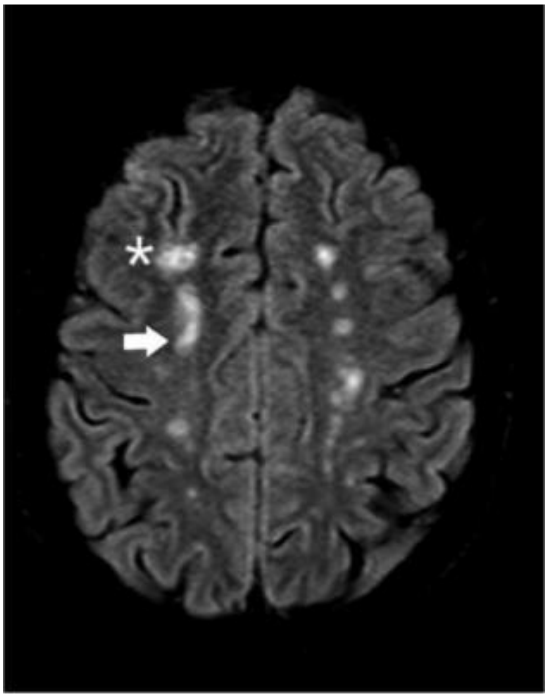

Figure 7. T2 FLAIR image in axial plane showing white matter lesions in semiovale centers (white arrow), with a lesion affecting subcortical U-fibers (*).

4.2 Lesion distribution

In 8.5% of patients. NL was presented in the brain. 38.3% with SL. 14.9% with MU lesions and 38.3% with MB lesions.

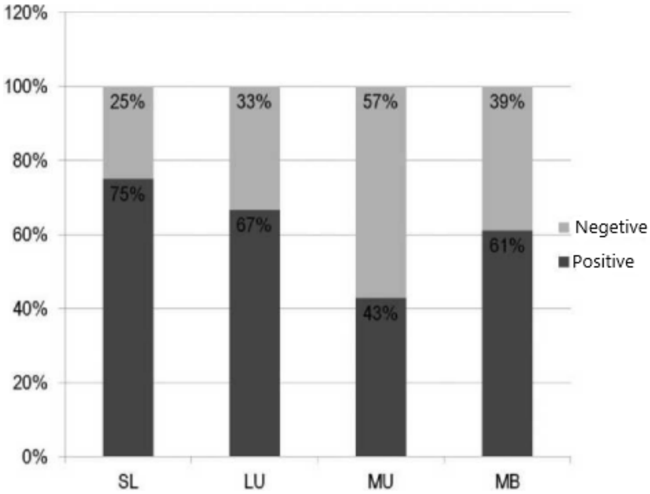

Figure 8. Lesion distribution. according to positive or negative HITS results. NL: no lesions. SL: single lesion. MU: multiple unilateral lesions. MB: multiple bilateral lesions.

They presented positive HITS: 75% of NL patients. 66.7% of SL. 42.9% of MU and 61.1% of MB (**Table 2** and **Figure 8**).

There were no statistically significant associations between lesion distribution and the presence of HITS. There are two situations that register p-values close to those required for significance. namely: The association of HITS-positive class C1 with SL (p 0.0911). and HITS-positive C2 and MB lesions (p 0.0649).

4.3 Affected vascular territory

Taking into account that two or more affected vascular territories may coexist in the same patient. we note that (**Table 2** and **Figure 9**):

Of the total patients. 68.1% had AC involvement. of whom 53.1% were HITS-positive and 46.9% HITS-negative. Of the patients with lesions in the CA. 52% of the patients with ACA involvement and 54.29% with MCA involvement were HITS-positive.

Of the total patients, 44.7% had involvement of the PC, of which 61.9% were HITS-positive and 38.1% HITS-negative. Of the patients with lesions in the PC, they showed HITS-positive: 64.3% of the patients had involvement of the AT and 55.6% of the AC.

We highlight that we found a statistically significant difference between patients with HITS- positive class C2 and the presence of lesions located at

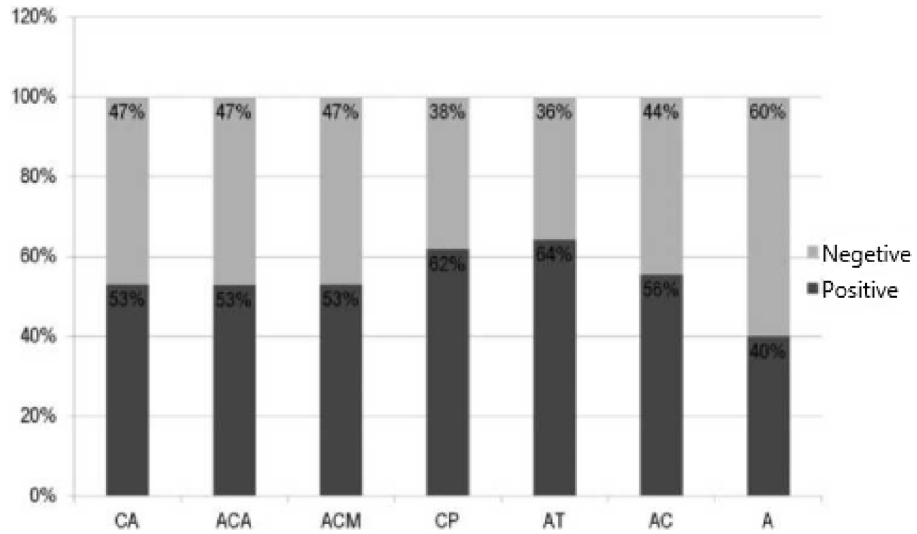

Figure 9. Vascular territory affected by the lesion. according to positive or negative HITS results. CA: anterior circulation. ACA: anterior cerebral artery. MCA: middle cerebral artery. PC: posterior circulation. TA: brainstem arteries. CA: cerebellar arteries. A: both (CAand PC).

the level of the PC (0.0275). No other statistically significant differences were found between the vascular territory affected and the presence or absence of HITS.

On the other hand, we observed that the most frequent lesion location in HITS-positive patients is at the level of subcortical U-fibers. We observed that the majority of HITS-positive patients with SC lesions (72%). had no cardiovascular RF. and only 28% had relevant RF (p 0.2111-not significant). Similarly. the majority of HITS-positive patients with MB lesions (79%) had no RF and only 21% had relevant RFs (p 0.1985-not significant).

5. Discussion

Although the MRI study protocol included DWI sequences and ADC map for the detection of acute lesions. in our study. as in that of Huang[25]. FLAIR sequences have been used for the analysis of the location of recent and old ischemic lesions. The additional sequences helped to characterize the lesions and to select those oriented to an embolic cause.

Regarding lesion location. Boutet[26] has described a statistically significant relationship between patients with PFO and lesions located at the level of the subcortical U-fibers. Such a relationship was also observed in other studies. Although not significantly[25,27-30], our findings are in agreement with those of Boutet[26] as 83.3% of patients with lesions at the SC level present HITS-positive and 16.7% HITS-negative (p 0.0294). We also observed a greater involvement of the ST level in HITS-positive patients (63.2%). although this was not statistically significant.

Regarding lesion distribution in MRI, the studies by Huang[25], Boutet[26], Lamy[27], Liu[28], Jauss[29], Santamarina[30] and Feurer[31] describe a bilateral distribution with multiple lesions in patients with PFO. a finding that agrees with the results obtained in our study (61.1% of MB lesions correspond to HITS-positive). Additionally. we have found a high proportion of patients with SL (66.7% of SL correspond to HITS-positive). None of them have been shown to be statistically significant. However. from these findings. it can be hypothesized that in patients younger than 65 years presenting multiple bilateral lesions or a single hyperintense lesion in FLAIR sequences with subcortical predominance. with no other apparent cause for the origin of the lesions. suggests the possibility of paradoxical embolism from a PFO as etiology. We should mention here that. although there is a high proportion of SL patients with positive HITS (75%). this value lacks relevance and statistical significance. since the total number of patients without lesions was very low (8.5%).

Regarding the vascular territories affected. most of the aforementioned studies describe a slightly greater involvement of the CA in patients with PFO (vascular territories of the ACA and MCA). although none of them has been able to establish a statistically significant association[25-28.31]. With respect to PC. three authors describe a statistically significant association with lesions caused by PFO: Boutet[26] in the posterior cerebral artery territory. Lamy[27] in the superior cerebellar artery territory. and Jauss[29] who considers the entire posterior circulation territory. Our findings reflect a non-significant predominance of CP involvement (61.9%) with respect to the CA (53.1%) in patients with HITS-positive. In this regard. we highlight that the subgroup of patients with moderate HITS (C2). showed a significant relationship (p 0.0275) with lesions in the PC. which is consistent with the observations described by Jauss[29].

Regarding the relationship between patients with cardiovascular RF and the presence of HITS. we can mention that. in our sample. when a patient had MB lesions of SC location. without RF to justify them. there was a greater probability that the lesions were due to PFO. It is likely that. due to the small sample size. the p values are not statistically significant (p 0.2111 for SC lesions and 0.1985 for MB lesions).

Of the studies mentioned above. all have been performed using images from 1.5 Tesla (T) MRIs. with the exception of Huang[25] which used a 3T MRI. The latter is the only study that assessed lesion load using the FLAIR sequence. supported by T2-weighted images as additional information. The other studies have used DWI sequences and ADC maps to assess lesions in acute stages, without considering old lesions visible by MRI[26,27,29-31]. Another study has considered lesions visible only on T2-weighted images. which. in our case. would have made it difficult to identify potential false positives. such as dilatations of peri-vascular Virchow-Robin spaces or to visualize periventricular or cortical lesions[28]. Our study protocol included. among others. T2-weighted sequences. DWI and also FLAIR. using the latter for lesion analysis. Like Handke[32], we did not find an association between the development of paradoxical embolisms due to PFO and the variable age.

Regarding the relationship between TCD and Transesophageal Echocardiogram (TEE) findings. in HITS-positive patients. 58% had PFO on TEE and 42% were negative. In HITS-negative patients. 100% had negative PFO on TEE (bilateral p-value 0.00035). If on TCD the result is HITS-negative. there is a statistically significant association with negative PFO (p 0.0003). If the HITS is positive. the association with PFO is statistically not significant. therefore. this situation should be confirmed with TEE.

Like most of the study groups mentioned. we have found the limitation of having a small sample size. which should be taken into account in the resulting statistical analysis in our work. Likewise. we believe that it is not possible to differentiate by means of MR images whether the lesions were due to paradoxical embolisms or cardioembolic sources. in which the literature describes a greater involvement of the anterior circulation. Another limitation of our study is the performance of TCD by a single observer. We consider it of interest for future studies to evaluate the inter-observer variability of the technique.

6. Conclusion

In patients younger than 65 years with a history of stroke and suspected FOP with positive HITS on TCD. brain MRI shows predominantly lesions at the level of subcortical U-fibers. These are usually SL or multiple lesions with bilaterally symmetrical distribution. In patients with moderate HITS. involvement of the posterior circulation vascular territory predominates.

Conflict of Interest

The authors declare that they have no conflict of interest.

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