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Cerebral Protection in Carotid Angioplasty – Is There a Need? Advantages and Disadvantages of Each Type of Protection Device

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Additional information is available at the end of the chapter

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1. Introduction

Currently, ischemic cerebral vascular accident (ICVA; stroke) is an illness with a high incidence and a high mortality rate [1,2]. In Brazil, depending on the state of the Brazilian Federation and the period analyzed, cerebrovascular disease is the leading cause of mortality [3]. Moreover, survivors present a continuous risk of developing serious complications [4]. Carotid atherosclerotic disease is the cause of approximately 15 to 20% of cerebrovascular accidents [5].

Carotid stenosis is present in 7% of men and 5% of women aged 65 years or older [6]. In serious cases (>70% stenosis), stenosis is an important cause of ICVA and transient ischemic attack (TIA). The estimated risk of ipsilateral ICVA in 5 years is 4% in the population without carotid stenosis; the risk increases to 18% in patients with asymptomatic stenosis above 75% and reaches 27% in symptomatic patients with stenosis >75% [7]. Several authors have described risk factors associated with carotid atherosclerosis, such as age, smoking, systemic arterial hypertension (SAH), hypercholesterolemia, coronary artery disease, peripheral vascular disease, and male gender [4,8,9].

2. Treatment of carotid stenosis

Treatment options for carotid stenosis include medication or surgery [10-12]. Clinical treatment includes antiplatelet agents and statins associated with the control of risk factors such as arterial hypertension, dyslipidemia, hyperglycemia, diabetes, and smoking [13]. Relevant studies comparing the outcomes of clinical treatment and surgery showed an important

reduction in the risk of CVA among the patients selected for surgical treatment. In the NASCET study, the risk of CVA was significantly reduced by surgery (9% in the surgical group versus 26% in the medication treatment) [10]. In another classical trial with asymptomatic patients, surgical treatment was also associated with a better prognosis (4.8% versus 10.6% for medication treatment) [14].

The two main effective treatment options for patients with serious carotid stenosis are carotid endarterectomy (CEA) and carotid angioplasty with stent (CAS). CEA was the first surgical option developed. It is indicated for symptomatic patients with carotid stenosis >60% and in centers with surgical risk below 6%. In asymptomatic patients, a degree of stenosis >70% is considered an indication for surgical treatment, but surgeons must notice morbi-mortality lower than 3% [10,14-17].

The most recent surgical option is CAS, which consists of an approach to stenosis through a natural route within the vessels. A flexible guide wire and catheter are inserted into the arterial system through a peripheral venipuncture and are maneuvered to the stenosis site, where the narrow portion is opened using the stent and balloon dilation.

CAS is considered less invasive than traditional surgery (CEA) and does not require an incision on the lateral side of the cervical region [18]. CAS also has the advantages of being able to maintain a steady flow of blood to the brain during CAS with a filter, generally using local anesthesia, and allowing early hospital discharge [18]. Thus, the indications for CAS are the same as those for CEA and also encompass other situations, such as comorbidities, occlusion of the contralateral carotid artery, high carotid bifurcation, concomitant distally associated stenosis, postradiotherapy stenosis, and restenosis after carotid endarterectomy [9,19,20].

The CREST trial compared CAS and CEA, examining complications, such as CVA, myocardial infarction, or death during CAS and CEA, and CVA four years after these techniques were applied. The authors observed similar rates of complications between CAS and CEA and concluded that the techniques are equivalent in terms of short- and long-term clinical results, but CAS carries a higher risk of ICVA and CEA carries a higher risk of heart attack during the periprocedural period. This study also found that good results might be influenced by good treatment and the expertise of the interventionists and surgeons [12].

Currently, CAS is considered a safe and effective technique for treating stenosis in the carotid artery >70% in symptomatic patients, when assessed by noninvasive methods, and >50% when assessed by catheter angiography, as indicated by the guidelines of the American Stroke Association (ASA; Class I recommendation with evidence level B) [21].

The first angioplasty for carotid stenosis was performed by Mathis in 1979 in a patient with fibromuscular dysplasia that caused symptomatic carotid stenosis [22]. The first angioplasty for atherosclerotic lesions was reported in 1980 by Kerber et al. [23]. The first series of carotid angioplasties was published in 1987 by Theron et al. and included 11 patients [24]. At the beginning of the 1980s, publications regarding the use of balloon occlusion in the carotid artery to reduce embolic complications began to appear [24-26].

The first balloon-expandable stent was used in a carotid artery in 1989; however, these early stent models were prone to extrinsic compression and deformation. In this group of stents,

adverse effects occurred in more than 10% of patients within the short 30-day follow-up [27,28]. Subsequently, deformation was avoided using the self-expandable Wallstent® stent [29] and later by self-expandable nitinol alloy stents. However, the risk of cerebral embolism remained, although it was reduced compared with the risk associated with the first stents. Restenosis, which occurred frequently after angioplasties without a stent, was reduced drastically. Currently, all manufacturers of endovascular intervention materials produce stents with rapid self-expanding technology compatible with the thin 0.014-inch guides common to most cerebral protection systems [13]. Nonetheless, carotid stenosis treatment with either CAS with cerebral protection or with CEA continues to carry an inherent risk of embolism.

3. Is there a difference between materials used in carotid angioplasty?

As the CREST Trial showed, the risk of ICVA in CAS is a technical problem that remains unsolved [12]. A heavily debated topic in the literature is the design of the metallic alloy used to outline the empty spaces, which are called cells. Different types of frames for the metal skeleton can promote plaque stabilization, depending on the size of the free area between the metal brackets. Stents with a braided metallic mesh, which are dense throughout, can be more effective at covering the plaque and reducing the risk of embolism [30]. These closed-cell stents are characterized by small cells (areas enclosed by metal) joined together (Figure 1). Segmental rings connected to each other by points that are welded together and large areas that are not covered by metal are called open-cell stents [30]. Hybrid stents, which have a closed-cell design in their central part and an open-cell design in their proximal and distal parts, can also be found. These stents are rarely used in practice.

There are several examples of closed-cell stents, such as Wallstent® (Boston Scientific), Xact® (Abbott), and NexStent® (Endotex). The Carotid Wallstent® is considered the prototype for closed-cell design stents. Examples of stents with an open-cell design include Protégé® (Ev3), Precise® (Cordis), Acculink® (Abbott), and Exponent® (Medtronic). The Carotid Wallstent® model is manufactured with a stainless steel alloy and a closed-cell mesh, which may help to prevent embolic complications. Because of its design, the Carotid Wallstent® (Boston Scientific) undergoes a shortening by approximately 30% [31], and caution must be used when estimating its length. The Precise® (Cordis) stent is a nickel and titanium alloy (nitinol®) mounted on rings, which promotes an open-cell aspect and offers great flexibility. The Protégé® (Ev3) stent also uses nitinol and an open-cell design, and both conical and straight versions are available. These last two stents cannot be collected after they begin to release; therefore, they should only be opened when the implant site is certain. However, these stents do not undergo shortening.

A study by Tadros et al. used photomicroscopy to analyze debris found in the filters after CAS and showed that open-cell stents are associated with a larger mean particle size compared with closed-cell stents [32].

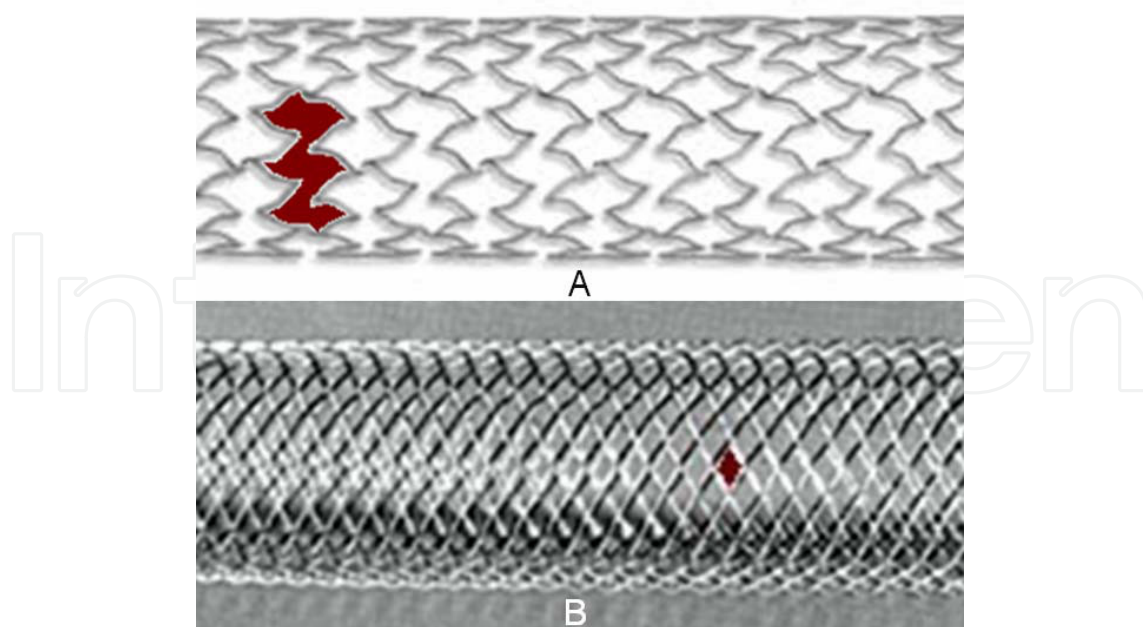


Figure 1. Typical arrangement of the metal mesh of an open-cell stent (A) and a closed-cell stent (B). The area of a cell in each type of stent is highlighted in red

The results for angioplasty should be analyzed considering that there are ongoing major evolutions in methods and materials. The results of angioplasties after the introduction of stents and cerebral protection systems cannot be compared with the results of studies conducted before the development of these materials [13,32-37].

Although the initial purpose of carotid stenosis treatment is the prevention of cerebral infarction, both CEA and CAS carry risks of causing infarcts [13]. The materials and techniques have been modified to reduce the risk of embolic complications during CAS. Several authors [32-38] have shown the rare relative incidence of cerebral embolism and death after carotid angioplasty with or without cerebral protection.

Our experience with carotid angioplasty began in 1998 and 2000. At that time, cerebral protection systems were not available in Brazil. During this period, 72 CAS were performed, and the combination of neurological complications and death reached 5.5%. In the subsequent period (2001 to 2007), 1215 CASs were performed with filters for cerebral protection, and our occurrence of neurological complications and death fell to 1.8% [38].

Although some authors defend the use of CAS without cerebral protection, we emphasize that symptomatic embolism is rare and that the use of safety devices, such as cerebral protection systems, functions as a reserve parachute: Although they are rarely needed, no one wants to jump without one (recommendation class IIa, level of evidence: C, [39]).

Currently, several devices are capable of providing cerebral protection during carotid stenosis treatment, but the morbimortality results differ for each device. The forms of protection for each device are also different. Nonetheless, other authors using various methods (most notably

Doppler and MRI) have shown that an enormous load of emboli to the brain may not determine symptoms. This phenomenon is called an asymptomatic embolism associated with CAS.

There are two types of cerebral protection systems: proximal and distal. The protection systems with filters are distal, and the protection devices with balloons can be proximal or distal. Proximal devices have the theoretical advantage of exerting protection during all phases of intervention, except during the positioning of the guide catheter or the long sheath. The proximal devices use temporary occlusion of the common carotid artery with a balloon, and a second balloon occludes the external carotid artery, resulting in the stagnation or reversal of the flow of the internal carotid artery (example: the PAES® Parodi antiembolism system). With this type of device, protection is initiated before the stenosis is crossed with the guide wire, which can reduce the risk of distal embolization. After the stent is implanted, the blood is aspirated from the carotid bifurcation to remove any fragments, and later, the proximal protection device is removed [40-42].

In contrast, with the distal devices, it is necessary to cross the stenosis with the microguide and then to use the distal device on the lesion. Therefore, the distal systems consist of a device (filter or balloon) with an integrated guide wire. This set-up allows the CAS to be performed along the guide wire. With the distal protection, embolization can occur when the guide catheter or sheath is positioned and during the passage of the guide wire through the stenosis before the distal device enters the action.

Distal protection systems allow two different forms of approach. One form is the occlusion of the distal cervical internal carotid artery by a balloon (example: PercuSurge®). With this type of system, there is a complete interruption of the antegrade flow, which provides protection for the particles that do not reach the brain. After the CAS, manual aspiration is performed, the balloon is deflated, and the system is removed [43,44].

The other form of distal protection is through the use of a filter (examples: EPI®, Angioguard®, Spider®). In this device, the filter (Figure 2) crosses the stenosis and is implanted in the distal cervical portion of the internal carotid artery. The stent and balloon are introduced over the guide to perform the CAS. There are different types of filters, but the aim of all of them is to retain particles, thereby preventing embolisms from reaching the brain and maintaining continuous blood flow. At the end of CAS, the filter is closed and removed from the patient with the embolic material inside [13]. In terms of design, the filters can be concentric (examples: Emboshield® and Angioguard® Cordis) or eccentric (examples: Filterwire EPI/EZ® Boston Scientific/Target and Spider®eV3). In concentric filters, the metallic guide occupies the center of the structure. In eccentric systems, the guide is outside the center of the protection device [45,46].

Thus, the two main types of cerebral protection devices used in CAS are filters that allow distal flow during the CAS and systems for the temporary occlusion of the carotid artery (balloons) that promote the inversion or paralysis of flow to the brain. Some authors defend filtering devices, but others defend the balloons because they are believed to offer more complete protection of the brain. Furthermore, the use of these cerebral protection systems is not supported in some patients.

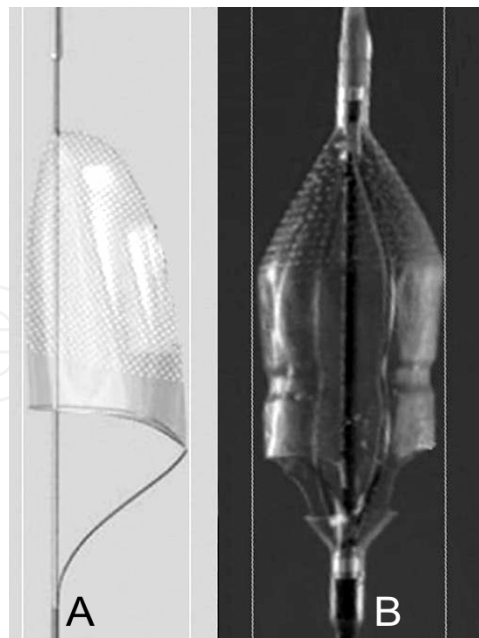


Figure 2. Examples of cerebral protection devices: eccentric design (A) in the EPI® filter and concentric design (B) in the Emboshield® system

Although all devices have a common goal of preventing the entry of particles into distal circulation, the perfect protection system does not exist [42]. Among proximal protection systems with balloons, arterial occlusion is the weakest point because patients might not tolerate it. Moreover, the contrast of vessels during the CAS is difficult because of flow stagnation, which makes positioning the stent difficult. Moreover, this system is more laborious and complex to use than filters. Additionally, proximal protection systems are very high profile and tend to lead to hemorrhaging complications at the puncture site. The device's advantages include its ability to initiate cerebral protection at an early stage and to avoid embolization during the initial passage of the wire through the stenosis [13,42].

The distal embolic protection devices with a balloon have the disadvantage of preventing antegrade flow, which renders some patients intolerant of this type of device. The balloon may also cause vascular lesions (example: pseudoaneurysm), and the affixture of the balloon may be lost during the CAS. Moreover, images cannot be easily obtained while the balloon is in use and, technically, the balloon is not very maneuverable. An advantage of distal protection devices is their ease of use compared with proximal occlusion balloons [13].

Among the disadvantages of distal embolic protection devices with filters is that they may not capture all particles and their delivery and recovery systems may cause embolisms. Some filters may attach to the stent because of bad handling. The advantages of filters include the preservation of antegrade flow to the brain during all stages of the CAS and the ability to obtain graphic images easily. Some systems allow the operator to select which guide wire to use to cross the lesion, which allows the filter to remain in contact with the arterial wall and the guide wire to be moved during the CAS without mobilizing the filter [13].

An advantage of using filters is their ability to maintain constant flow to the brain during all stages of the angioplasty, unlike protection balloons, which promote the temporary halt of flow to the brain. Carotid filters are also easier to use than occlusive or reverse flow protection balloons.

4. Cerebral embolism in the surgical treatment of carotid stenosis

Despite the advantages of cerebral protection systems, Müller-Huelsbeck et al., in their 2005 study of ex vivo pig carotid arteries with four types of filters and one type of cerebral protection balloon, found that particles were passed with all of the protection systems tested [47]. Piñero et al. [48], using the transcranial Doppler technique, observed signs of embolism during several phases of CAS, including the initial unprotected phase. Similarly, Schmidt et al. [49] divided the carotid angioplasty into five phases from start to finish. This comparative study used one type of filter (EPI®) and one type of occlusive system with balloons (MO.MA®) and found that particles were passed in all phases of both systems.

The transcranial Doppler tool can help identify signs of embolism during an unprotected phase (before using the filter) or during the passage of the filter, and it can identify embolisms when the stent or balloon is applied or the filter is removed [50,51]. The transcranial Doppler can provide information about the flow in the polygon vessels [52] and show changes in the cervical segment after angioplasty [53]. However, the Doppler assessment has the disadvantage of evaluating only one vessel, usually the middle cerebral artery or the distal cervical internal carotid artery on the carotid stenosis side, leaving a vast territory of the brain uncovered during the evaluation of embolic phenomena. No correlation can be observed between the quantity of microemboli identified during ultrasound and new embolism outbreaks found during MRI [54]. In contrast, MRI can evaluate the entire encephalon, which is particularly important because embolic events may occur during the CAS or during the angiography preceding CAS in other areas of the brain supplied by the carotid undergoing CAS [46,48].

According to several authors, the use of cerebral protection systems is an important factor in reducing the risk of cerebral infarction during CAS [9,13,34,55]. However, although most patients are asymptomatic after CAS, signs of embolism can be detected using the transcranial Doppler technique and MRI [56] because of different factors, such as the existence of pores in the protection systems that allow particles up to 100 microns pass, the manipulation of the artery before the filter is opened, the filter not adapting to the artery wall, and crucially, a lack of proper training in handling the systems [46,48,49,54,57-63].

5. Imaging evaluation of cerebral embolism

We consider MRI an excellent method for evaluating cerebral ischemia in its various presentations. An MRI study of various acute neurological presentations of an ischemic nature includes several forms of ischemia presentation on the images [64].

Diffusion (DWI) is the best MRI technique to differentiate ischemia from chronic infarction. While the latter shows an increase in diffusion, the former classically restricts diffusion [65]. The identification of acute lesions in patients with multiple chronic lesions makes DWI a tool of unquestionable value in current imaging practice.

Water in tissues has a randomized translational movement ("Brownian motion") in its molecules caused by thermodynamic energy and the viscosity of the medium. This type of movement is related to CDA, and MRI uses DWI to evaluate it [66,67].

Diffusion imaging is sensitive to the microscopic movement of water protons. Water protons undergo a change during the transverse magnetization phase in the presence of a magnetic field gradient. Thus, areas with greater diffusion (faster movement) are subject to a high degree of signal attenuation compared with areas with lower diffusion (slow/restricted movement), which show lower signal attenuation. Animals subjected to occlusion of the middle cerebral artery (MCA) showed signs of ischemia in diffusion within 45 minutes. These findings are believed to reflect the restriction of water movement by the cellular membrane. MRI's greater sensitivity for detecting acute ischemia in diffusion is believed to be a result of the movement of water within the cell, which restricts the movement of water protons (cytotoxic edema), while the T2-weighted images show a signal change that results mainly from vasogenic edema. It is estimated that cytotoxic edema begins very soon after ischemic abuse, while the vasogenic edema begins to develop 6 hours after the ischemic incident.

Moseley et al. [65] argued that significant diffusion decrease (restriction or reduction) in ischemia reflects the deviation of an environment with extracellular water protons with a faster diffusion to a more restricted intracellular environment, in addition to the depletion of the sodium-potassium pump in the cellular membrane because of infarction. The cytotoxic edema is thus responsible for reducing diffusion during ischemia.

Nonetheless, the diffusion of ischemia areas can be reversed after early reperfusion and are potentially reversible if they occur after CAS. It has also been shown that ischemic lesions in diffusion might not leave changes that appear in later MRI scans after TIA frames.

The embolic complications identified in DWI occur more frequently than the apparent low rate of clinical complications would suggest. An MRI may quantify the ischemic foci, making it an important method for validating the advantages and complications of CAS.

To examine this issue more deeply, we conducted a prospective randomized study (patients chosen randomly from the outpatient neuroradiology service of INCOR) in a case-control setting [68]. We used angiographic exams and MRI studies that showed cerebral embolism represented by the diffusion sequence (DWI) before and after surgical endovascular treatment to quantify, locate, and measure new restriction foci in diffusion MRI and to correlate the new DWI restriction foci with demographic aspects (gender, age, side of the carotid treated, and symptoms), risk factors for cerebrovascular disease, aspects of the angioplasty technique used, and the presence of previous infarcts in MRI.

6. Methods

Our sample consisted of 40 patients presenting carotid stenosis of atherosclerotic origin. The patients were referred for MRI exams with diffusion techniques before and after CAS. All of the patients in this prospective study signed an informed consent form. The inclusion criteria were as follows: patients with serious carotid stenosis (shown by Doppler, ATC, or digital subtraction angiography [DSA]) who were referred for endovascular treatment for carotid atheromatous disease according to the local institutional guidelines, who agreed to participate in the research protocol, and who had MRI studies conducted with diffusion techniques at most 24 hours before and up to 72 hours after the CAS with a protection filter.

Exclusion criteria were the following: intra-arterial thrombi observed in the angiography before CAS; patients with disabling complications from previous cerebral infarcts; contraindications for the MRI scan, such as a cardiac pacemaker or claustrophobia, patients with macroemboli in the DSA after CAS, clinical conditions compatible with ischemia after CAS, angiographic exam showing stenosis <60%, MRI exams with movement artifacts, and imaging studies with serious stenosis in the contralateral cervical carotid, vertebral arteries, or intracranial arteries.

Three patients out of 40 were excluded because they showed stenosis <60%, and one patient was excluded for having exceeded the maximum time established for MRI after CAS because of coronary angina and hemodynamic instability.

The MRI studies were performed using commercially available single high-field equipment (1.5 T, LX Horizon®, General Electric Healthcare) with a skull coil (“birdcage transmit/receive quadrature”).

The MRI scans before and after CAS followed the same sequencing protocol:

- Locator: 256x128 matrix, FOV 27 cm, 10 mm thickness, 5 mm spacing, number of acquisitions (“n_{ex}”): 1
- DWI: 128x128 matrix, FOV 22 cm, 5 mm thickness, 0 mm spacing, TE minimum 72.8 ms, TR 9000 ms, “b-value” 0 and 1000, diffusion direction: “all”, number of acquisitions: 2
- Coefficient of apparent diffusion: map of “ADC”
- T2W, axial, 288x224 matrix, FOV 22 cm, 6 mm thickness, 0.6 mm spacing, TE 102 ms, TR 4750 ms, echo train length 23, bandwidth 31.25 and number of acquisitions: 2
- T1W, axial, 256x192 matrix, FOV 22 cm, 6 mm thickness, 0.6 mm spacing, TE 14 ms, TR 475 ms, bandwidth 15.63 and number of acquisitions: 2
- Fluid-attenuated inversion recovery (FLAIR): axial, 256x192 matrix, FOV 22 cm, 6 mm thickness, 0.6 mm spacing, TE 96 ms, TR 10000 ms, TI 2.100 ms and number of acquisitions: 1
- T2W, coronal, 288x224 matrix, FOV 22 cm, 6 mm thickness, 0.6 mm spacing, TE 102 ms, TR 4750 ms, bandwidth 31.25 and number of acquisitions: 2

New foci (NF) of ischemia were defined as the presence of a hypersignal (restriction) in diffusion after CAS that was not present in the same sequence before CAS. These foci were considered recent, additional infarcts compared with the first MRI.

The opposite of a recent infarction caused by DWI after CAS is an old infarction that is present in the T2W sequencing of the MRI before CAS. Chronic cerebral infarction is the end result of prolonged ischemia. Areas of hypersignal in the cerebral parenchyma in the T2 sequence with areas corresponding to the variable signal in T1 (with the tendency to be isointense compared with the fluid in T1 and T2) without restriction in DWI and with no enhancement after paramagnetic contrast were considered old infarctions ("T2W infarction"). Other diseases that may have a signal aspect similar to that of old infarctions (for example: porencephalic cysts, arachnoid cysts, low-grade astrocytoma) were excluded from the count because of their topographic characteristics, their appearance on the edge of the lesion, or their appearance on the surrounding tissue or because they showed a signal that differed from that of the fluid in the other sequences in the MRI study.

The MRI images were analyzed by the consensus of two experienced neuroradiologists using the eFilm® software without access to the clinical data or angiography and CAS data. If there were discrepancies between the two neuroradiologists' findings, the studies were analyzed by a third observer to reach a consensus.

The NF were correlated with age, gender, side of carotid artery treated, presence of previous symptoms related to carotid stenosis, risk factors for atherosclerosis and ICVA (diabetes mellitus, systemic arterial hypertension, hypercholesterolemia, ischemic coronary artery disease, arrhythmia, ischemic peripheral vascular disease, transient ischemic attack [TIA], and ischemic cerebrovascular accident [ICVA]), percentage of carotid stenosis, presence of ulcers in the atheromatous plaque, previous infarction noted on the MRI, number of catheters used, number of arteries on which angiographies were performed, contralateral carotid occlusion, endovascular access technique used to reach the common carotid artery on the side of the angioplasty, type of filter, type of stent, volume of contrast used in the CAS and angiography, fluoroscopy time spent during the procedure, and the localization, number, and diameter of these NF. These parameters were also correlated between patients with only one NF and those with multiple NFs.

The localization (laterality) of the encephalic NF was defined as ipsilateral if it coincided with the area supplied by the carotid artery undergoing angioplasty. The localization of the NF was defined as contralateral if the cerebral area did not coincide with the side of the CAS, meaning the area was nourished by the carotid artery contralateral to the angioplasty or the area located on the posterior fossa. In cases when it was impossible to determine laterality, the patient was excluded from the analysis, which occurred with two patients. Patients 16 and 27 showed stenosis in the carotid artery (left) and contralateral occlusion (right), with NF identified in the area supplied by the right carotid artery. Under this condition, the flow to the carotid area can use the anastomotic Willis polygon or openings in other collateral pathways can be determined (for example: flow through the vasa vasorum or retrograde flow through the ophthalmic artery). Thus, with NF in the area of the occluded artery, it is not possible to say with certainty whether the embolism originated directly in the CAS or migrated through the anastomosis of areas that revascularized the cerebral territory of the occluded carotid artery. Because of the

difficulty of relating the localization of the embolism precisely with the artery that underwent angioplasty, we decided not to include these two cases in the analysis of laterality.

The diameter of each NF was noted using the maximum diameter of the lesion in the DWI sequence through a metric analysis determined manually in the software (eFilm®). For comparison, the NFs were divided into three groups of diameters (<5 mm, between 5 and 10 mm and >10 mm) according to the stratification method published by other authors [69,70].

The patients with carotid occlusion contralateral to the CAS were noted. To mark the occlusion of the internal carotid artery, we used DSA or MRI. In the absence of DSA in the carotid artery, we defined occlusion using MRI when there was no “flow-void” phenomenon and a high intravascular signal in the FLAIR sequence, compatible with thrombus in sections focusing on the internal intracranial carotid artery. Both imaging methods were accepted as sufficient for proving that a vessel was occluded.

Areas with DWI restriction after CAS (ischemia indicators) were correlated with demographic aspects, aspects of the angioplasty technique, stenosis characteristics, and the presence of previous infarctions on MRI. The quantification of stenosis in the carotid bulb studied was using the NASCET method [10] with DSA in all cases.

7. Angioplasty technique used

The patients were divided into two groups: “brief” angiography and “complete” angiography. An angiographic exam before CAS is conventionally called a brief angiography when the exam only includes an angiography of the carotid artery that is a candidate for treatment. A complete angiography includes the study of other cervical arteries or the aortic arch.

Antiplatelet therapy was standardized, and all patients received 75 mg clopidogrel and 100 mg acetylsalicylic acid orally on a daily basis, beginning at least five days before the procedure.

In the preparation of the materials, all of the introducers, catheters, and sheaths were pre-washed with physiologic saline flow and subsequently packed in a sterile container with physiologic serum and heparin before arterial puncture.

Under local anesthesia and light sedation from the anesthesiologist, arterial puncture was performed and the valved introducer was deployed in the common femoral artery, which was fixed to the skin with a wire suture for safety. If there was significant tortuosity of the iliac and femoral vessels, long introducers were sufficient to help stabilize the catheter and the catheter guide in the common carotid arteries.

A bolus injection of 10,000 units of heparin was administered intravenously after the valved introducer was installed. An atropine solution was prepared before the angioplasty and stored until the stent’s release. Intermittent verbal communication was maintained with the patient during the procedure by the doctors performing the CAS, as in the eventual clinical tests.

In all cases, the angiography of the carotid artery undergoing CAS was initially performed with a 5 Fr angiographic catheter to confirm the stenosis shown with other methods. At this point in the procedure, angiographies of the cerebral vessels nourished by the carotid artery

were performed, and they were repeated at the end of the CAS to observe any possible arterial occlusion. In all cases, a nonionic contrast with low osmolarity was used.

In all cases (n=36), an 8 Fr-caliber guide catheter was introduced into the common femoral artery inside the valved introducer, and the distal extremity was positioned in the common carotid artery undergoing CAS a few centimeters below the atherosclerotic plaque.

The possible methods for positioning the catheter guide safely in the common carotid artery, close to the bulb, were defined as access techniques. The endovascular techniques for accessing the carotid artery to be treated included direct access (DA), an exchange with the guide wire in the external carotid artery (ECA), exchange with the guide wire in the common carotid artery (ECC), and triaxial access (TRI). For the direct access technique (DA), the catheter guide was introduced into the common carotid artery by sliding it over a guide wire (0.035 inches) that had previously been placed in the artery.

The technique involving exchange with the guide in the external carotid artery (EEC) was as follows: the tip of the guide wire (0.035 inches) was positioned in the external carotid artery using a diagnostic catheter with a 5-Fr caliber (figure 3). It remained safely in this position without colliding with the atheromatous plaque, providing a means for the catheter guide to advance over the guide until it reached the common carotid artery. The ECC technique was defined as when the guide was positioned in the common carotid artery, rather than the external carotid artery, with the help of a catheter guide contained within a diagnostic catheter. At this point, the catheter was removed, and the catheter guide reached the common carotid artery by going over the guide. The TRI technique involved using a guide catheter with a diagnostic catheter inside (the designs and materials varied for each case) and a guide (0.035 inches) placed inside the diagnostic catheter. The catheter was free to attempt several maneuvers before the catheter guide penetrated the carotid artery for the angioplasty.

After positioning the catheter guide in the common carotid artery, one of the closed filter cerebral protection systems can be extended beyond the stenosis by positioning it a few centimeters above the stenosis close to the base of the skull, preferably in a rectilinear segment open in this topography. We also observed whether the filter was adjusted to the size of the artery to avoid dislocating the filter system during the subsequent maneuvers.

“Rapid exchange” filter systems were used, which consisted of a 0.014-inch microguide with a polyurethane membrane filter with 100 to 140 μm pores (100 μm in AngioGuard® filters [Cordis], 110 μm in EPI FilterWire EPI/EZ® filters [Boston Scientific/Target], and 140 μm in EmboShield® filters [Abbott]).

All of the patients were scheduled for the primary technique (without prior dilation of the stenosis via a balloon) using a stent with an appropriate diameter (7 to 8 mm) for each case and sufficient length to cover the bulb and the entire atherosclerotic plaque distally and inferiorly (at least 1 cm).

Self-expandable stents (Carotid Wallstent®, Boston Scientific/Target; Precise®, Cordis; and Protége®, ev3) designed for carotid use in a 0.014-inch guide system were used. Only the straight version of the Protége® stent was used in our study.

After the stent was released, 0.5 mg of atropine was administered intravenously. After tachycardia was observed, a catheter balloon was inserted and inflated inside the stent. The angioplasty balloon had the function of shaping the stent smoothly. The same balloon size was used for all of the procedures: 6 mm in diameter and 20 mm in length (Gazele®, Boston Scientific/Target and Amiaa®, Cordis). In this study, after the balloon was deflated, an immediate-control cervical angioplasty was conducted with a smooth manual injection of the contrast medium to avoid disturbing the filter and possibly mobilizing any waste that it retained.

Once control via cervical DSA at the end of the CAS was considered satisfactory (residual stenosis at a maximum of 30%), the filter was collected. Later, after the removal of the filter and the last stage of CAS, carotid angiographies for intracranial vascularization were performed in anteroposterior (AP) and profile to show that the artery subjected to CAS remained patent. Additionally, the intracranial vessels were thoroughly studied and compared with the preangioplasty angiograms to detect any macroemboli. The catheter guide was removed at the end of the CAS, leaving only the arterial introducer in the inguinal region. Heparin was not antagonized. After the CAS, the cases were monitored in the intermediate intensive care unit for 12 to 24 hours with attention to the patient's neurological state and especially his/her blood pressure.

All of the procedures were performed by an experienced neuroradiologist (with over 20 years of specialty experience) with the help of one or two residents. No patient showed any neurological or other symptoms after the CAS. The follow-up for clinical observations was the in-hospital period of four days.

The data were analyzed using several methods and logistic regression analysis. All cases were evaluated using SPSS (Version 15.0). A p-value <0.005 was considered statistically significant.

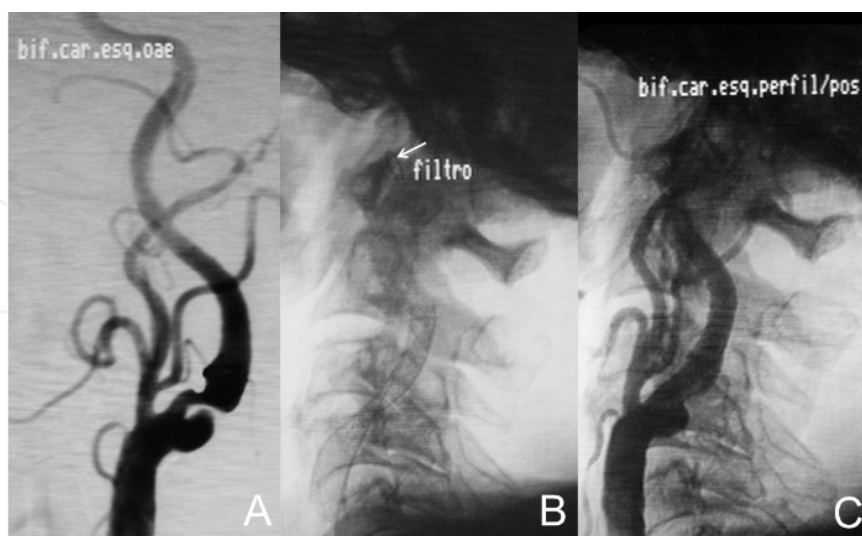


Figure 3. Patient number 2, 70 years old, male with diabetes, hypertension and coronary ischemia, displayed transient ischemic attack. . DWI exam after CAS (not shown) did not reveal microusemboli. Angiography showed stenosis of 70% (A) in the left carotid artery with additional imaging (ulcer). EPI® open carotid filter (arrow) and Wallstent (7 x 40 mm) self-expandable stent (B). Control angiography after CAS (C)

8. Clinical and demographic data for patients before CAS

Of the 40 patients who began the study, 36 completed the protocol. Their ages varied from 54 to 87 years (average: 72.08 years).

| | n (%) |
|--|---------------------|
| n of patients | 36 (100.00) |
| Male | 25 (69.44) |
| Female | 11 (30.56) |
| Right carotid artery | 15 (41.67) |
| Left carotid artery | 21 (58.33) |
| Symptomatic patients | 27 (75.00) |
| Asymptomatic patients | 09 (25.00) |
| Average age/standard deviation (years) | 72.08 (\pm 8.30) |

Table 1. Distribution of demographic data for the 36 patients

| Risk factors | n (%) |
|----------------------------------|------------|
| TIA | 17 (47.22) |
| ICVA | 11 (30.56) |
| TIA or ICVA | 26 (72.22) |
| Arrhythmia | 04 (11.11) |
| Ischemic coronary artery disease | 09 (25.00) |
| Diabetes | 12 (33.33) |
| Peripheral vascular disease | 19 (52.70) |
| Hypercholesterolemia | 12 (33.33) |
| Hypertension | 32 (88.88) |
| TOTAL | 116 |

Table 2. Distribution of risk factors (n=36 patients)

9. Data from the procedures and technical considerations of digital subtraction angiography and carotid angioplasty with a stent

| | |
|---|-------------------------------------|
| Degree of stenosis ¹ – average (variation) | 76.31% (60-99%) |
| Ulcerated plaques – n (%) | 14 (38.89%) |
| Contralateral carotid occlusion – n (%) | 7 (17.95%) |
| “Broad” examn (%) | 24 (66.67%) |
| “Brief” examn (%) | 12 (33.33%) |
| Filter – n (%): Angioguard® | 4 (11.11%) |
| Emboshield® | 7 (19.44%) |
| EPI® | 25 (69.44%) |
| Stent – n (%): Precise® | 9 (25.00%) |
| Protégé® | 5 (13.89%) |
| Wallstent® | 22 (61.11%) |
| Catheterization technique – n Direct access | 12 |
| Exchange in the external carotid artery | 10 |
| Exchange in the common carotid artery | 11 |
| Triaxial | 08 |
| Fluoroscopy time (minutes; average) | 665; 22.93 min/CAS ² |
| N of catheters used (n; average) | 83; 2.31 cat/patient |
| Contrast volume (milliliters; average) | 5480 ml; 182.67 ml/CAS ³ |
| Vessels submitted to DSA (n; average) | 106; average 2.94 |

¹ Percentage of stenosis evaluated by angiography

² Regarding fluoroscopy time, only 29 procedures were recorded (n=29). In seven patients, there were technical problems that prevented precise measurement.

³ For contrast volume, only 30 procedures were recorded (n=30). In six patients, there were technical problems that prevented precise measurement.

Table 3. Technical aspects and characteristics of the angiographic exams (n=36)

10. Imaging results

10.1. Aspects of MRI before the CAS

The preliminary MRI study before CAS showed six restriction foci in diffusion in four (11.11%) patients (Table 4 and Figure 4). These foci were not recorded as NF after CAS.

| | n (%) patients |
|--|----------------|
| Infarctions in T2 | 23 (63.9) |
| Foci of restriction in DWI (1 ^a MR) | 4 (11.1) |

Table 4. MRI data before CAS (n = 36)

Among the restriction foci in DWI before CAS, five out of six (83.33%) were ipsilateral to the carotid artery for CAS, and only one focus was not ipsilateral to the carotid that was treated (cerebellum). All hypersignal foci in DWI before CAS occurred in patients with symptomatic stenosis.

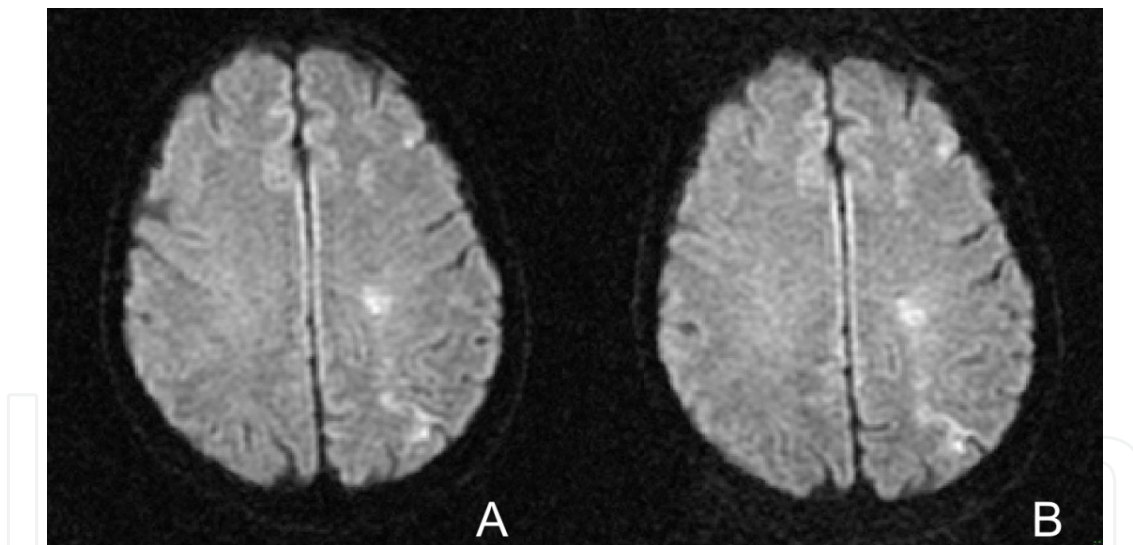


Figure 4. Patient number 7, male, 60 years old, underwent angioplasty of the left carotid artery. Restriction foci in DWI in the MRI scan before CAS (A). Manifestation found in 11.11% of patients. No NF were observed after CAS (B)

11. Aspects of MRI after CAS

There were no new areas of cerebral infarction after CAS in the analysis of conventional MRI sequences.

A comparison between the MRI diffusion sequences acquired before and after angioplasty showed 59 NF of restriction compatible with cerebral ischemia, which were distributed in 18/36 (50%) patients (Figures 5 and 6). The average NF in the 36 patients was 1.6 NF/patient (Table 5), and the diameter varied between 1 and 25 mm.

| | |
|---|------------------|
| NF number | 59 (18 patients) |
| NF size - n (%) | |
| <5 mm | 35 (59.33) |
| 5 – 10 mm | 19 (32.21) |
| >10 mm | 05 (8.46) |
| Vascular distribution (NF ¹) - n (%) | |
| Ipsilateral | 44 (77.19) |
| Contralateral | 13 (22.81) |
| pt – patient | |
| ¹ Two patients were excluded from the analysis of laterality | |

Table 5. Characteristics of new foci (NF) of hypersignal in DWI after angioplasty of the carotid artery

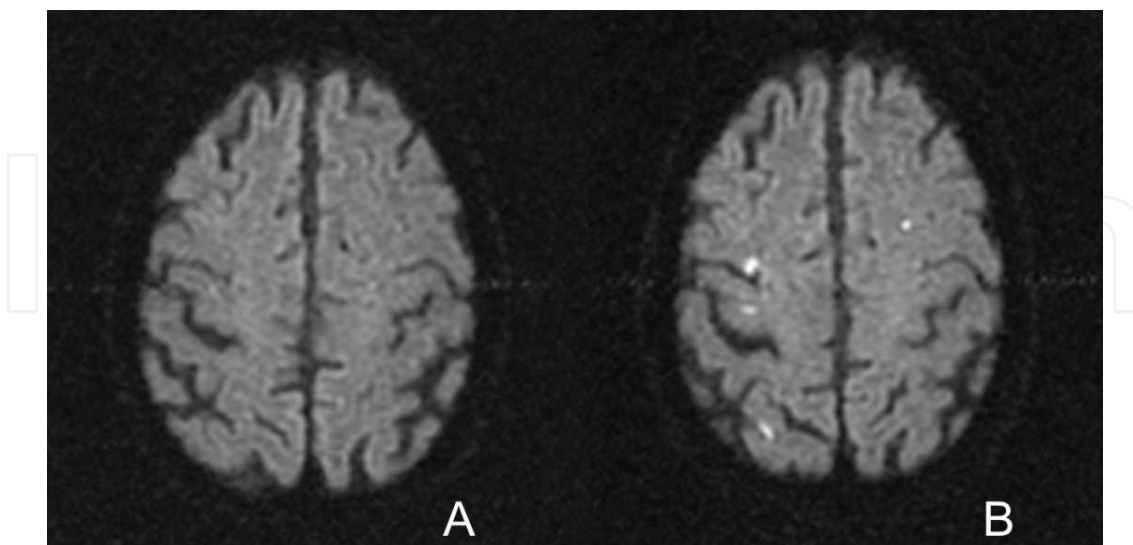


Figure 5. Patient number 9, 59 years old, underwent right CAS. DWI before CAS (A) without images of restriction. After CAS (B): ipsilateral NF (including primary motor rotation) and contralateral NF. Asymptomatic patient.

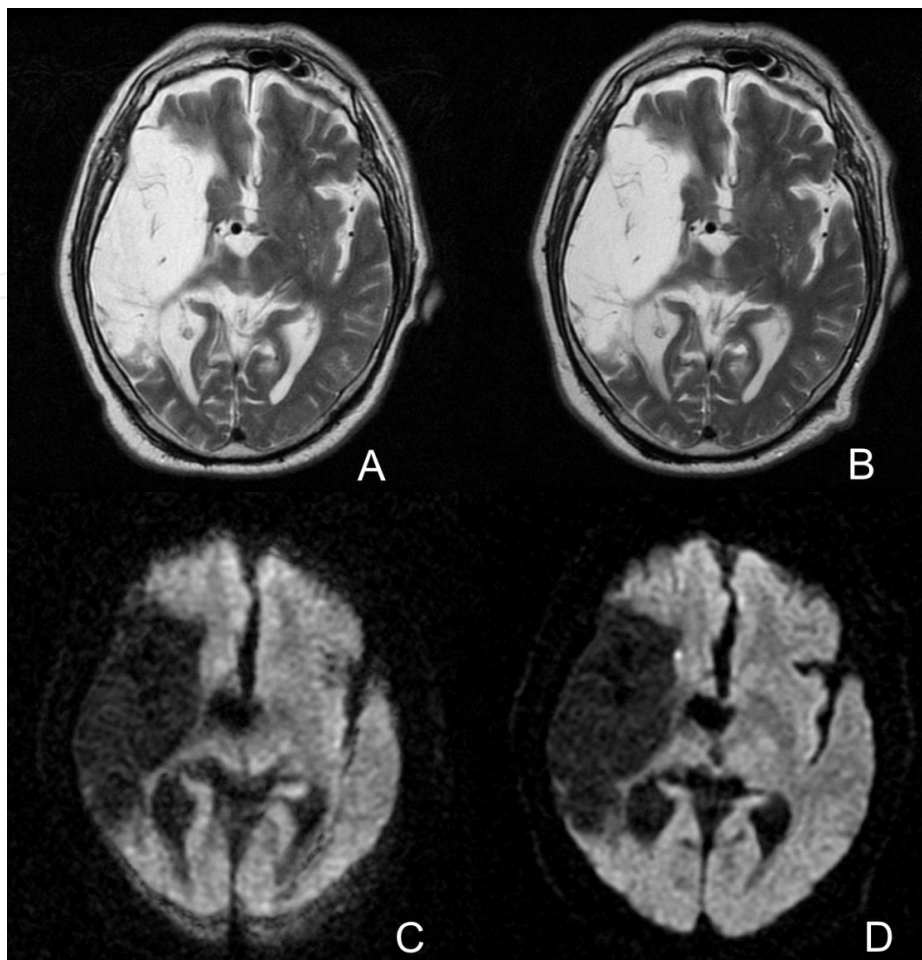


Figure 6. Patient 27, male, 73 years old with right carotid artery occlusion and stenosis of the left carotid artery estimated at 70% by DSA (not shown). Before CAS: T2 sequence (A) shows old infarction in the territory of the right MCA and diffusion sequence (C) without recent ischemia foci. The patient underwent DSA of both common carotid arteries and CAS of the left. In the MRI study, the T2 sequence was unchanged after CAS (B) and the DWI sequence showed NF in the head of the caudate nucleus to the right (D)

| Laterality of NF | % of NF | n of NF | Average ² | P |
|------------------|---------|---------|----------------------|-------|
| IP | 77.19 | 44 | 2.75 | |
| CL | 22.81 | 13 | 0.81 | 0.063 |
| Total | 100.00 | 57 | 3.56 | |

CL – NF contralateral to the area for CAS; IP – NF ipsilateral to the area for CAS

¹ Two patients were excluded from the analysis of laterality.

² NF/patients

Wilcoxon test

Table 6. Number and average of NF by laterality (n=16 patients¹)

| Presentation of NF per patient | n of NF | n of pt | Average (NF/pt) | SD | p |
|--------------------------------|---------|---------|-----------------|------|--------|
| Single NF (1 nf/ pt) | 9 | 9 | 1.00 | 0.00 | |
| Multiple NF (≥ 2 nf/pt) | 50 | 9 | 5.56 | 3.43 | <0,001 |
| TOTAL | 59 | 18 | | | |

pt – patient
Mann-Whitney U test

Table 7. Distribution of NF (single or multiple)

| Laterality | Number of patients | % of patients |
|--|--------------------|---------------|
| IP pure | 5 | 14.71 |
| CL pure | 5 | 14.71 |
| Intersection (IP+CL in the same patient) | 6 | 17.65 |

IP pure + intersection (IP+CL in the same patient)=11 patients=32.35%

IP pure: patients with only ipsilateral NF; CL pure: patients with only contralateral NF

¹ Two patients were excluded from the analysis of laterality.

No statistical test

Table 8. Distribution of NF based on laterality per patient (n=34 patients¹)

| Laterality by patient | n of NF | Average ² | p |
|-----------------------|---------|----------------------|-------|
| IP pure | 14 NF | 2.80 | |
| CL pure | 5 NF | 1.00 | 0.053 |
| Bilateral | 38 NF | 6.33 | |

IP pure: patients with only ipsilateral NF; CL pure: patients with only contralateral NF; Bilateral: patients with both ipsilateral and contralateral NF

¹ Two patients were excluded from the analysis of laterality.

² NF per case

Kruskal-Wallis test

Table 9. Number and average of NF according to laterality per patient (n=34 patients¹)

| NF after CAS | Average age (years) | SD | p |
|--------------|---------------------|------|-------|
| Without NF | 71.83 | 9.03 | |
| With NF | 72.33 | 7.75 | 0.855 |

Mann-Whitney U test

Table 10. Average and standard deviation of age in the groups with and without NF in the DWI after CAS.

| Factor | NF | | | | p |
|----------------|----|-------|-----|-------|-------|
| | No | | Yes | | |
| | n | % | n | % | |
| AGE (years) | | | | | |
| <75 | 8 | 44.4 | 7 | 38.9 | |
| ≥75 | 10 | 55.6 | 11 | 61.1 | 0.855 |
| TOTAL | 18 | 100.0 | 18 | 100.0 | |
| GENDER | | | | | |
| Male | 15 | 83.3 | 10 | 55.6 | |
| Female | 3 | 16.7 | 8 | 44.4 | 0.080 |
| TOTAL | 18 | 100.0 | 18 | 100.0 | |
| CAROTID ARTERY | | | | | |
| Right | 8 | 44.4 | 7 | 38.9 | |
| Left | 10 | 55.6 | 11 | 61.1 | 0.735 |
| TOTAL | 18 | 100.0 | 18 | 100.0 | |

Logistic regression analysis

Table 11. Distribution of age, gender, and side of the carotid artery treated based on the appearance of NF in the DWI after CAS.

| | NF | | | | p |
|-----------------------------------|---------------|-------------------------------|------------|-------------------------------|-------|
| | Yes | | No | | |
| | n factors | SD ² | n factors | SD ² | |
| Risk factors ¹ (n=116) | 60 | 1.75 | 56 | 1.18 | |
| | n of patients | Average (NF/pt ³) | n patients | Average (NF/pt ³) | |
| Patients (n=36) | 18 | 3.33 | 18 | 3.11 | 0.743 |

¹ Risk factors for atherosclerosis/ICVA

² Standard deviation for risk factors

³ Patient

Mann-Whitney U test

Table 12. Correlation of all risk factors with NF after CAS

| Risk factors | NF | | | | p |
|--------------|----|-------|-----|-------|-------|
| | No | | Yes | | |
| | N | % | n | % | |
| TIA | 8 | 44.44 | 9 | 50.00 | 0.800 |
| ICVA | 4 | 22.22 | 7 | 38.89 | 0.612 |
| ICVA or TIA | 12 | 66.67 | 14 | 77.78 | 0.845 |
| ARR | 2 | 11.11 | 2 | 11.11 | 1.000 |
| COL | 8 | 44.44 | 4 | 22.22 | 0.164 |
| COR | 4 | 22.22 | 5 | 27.78 | 0.701 |
| DM | 5 | 27.78 | 7 | 38.89 | 0.481 |
| PVD | 10 | 55.56 | 9 | 50.00 | 0.738 |
| HBP | 15 | 83.33 | 17 | 94.44 | 0.311 |

TIA: transient ischemic attack; ICVA: ischemic cerebral vascular accident; TIA or ICVA: cases with at least one ischemic condition; ARR: arrhythmia; COL: hypercholesterolemia; COR: ischemic coronary artery disease; DM: diabetes; PVD: peripheral vascular disease; HBP: high blood pressure

Logistic regression analysis

Table 13. Distribution of risk factors in relation to the appearance of NF after CAS

| Patients | NF | | | | p |
|--------------------|----------------------|-------|---------|--------|-------|
| | No | | Yes | | |
| | n of pt ¹ | % pt | n of pt | % pt | |
| Asymptomatic (n=9) | 7 | 77.8% | 2 | 22.2% | |
| Symptomatic (n=27) | 11 | 40.7% | 16 | 59.26% | 0.121 |

¹ Patient

Chi-squared test

Table 14. Occurrence of NF based on the presence of symptoms before CAS

| Clinical status of the patient before CAS | n of NF | % of NF | p |
|---|---------|---------|-------|
| Asymptomatic | 11 | 18.6 | |
| Symptomatic | 48 | 81.4 | 0.263 |
| TOTAL | 59 | 100.0 | |

Mann-Whitney U test

Table 15. Correlation between the presence of carotid disease symptoms before the procedure and the number of NF after CAS

| Infarct in T2 | NF | | | | p |
|---------------|-------------------|----------------|------|-------|-------|
| | No | | Yes | | |
| | n pt ¹ | % ² | n pt | % | |
| Without | 10 | 55.6 | 3 | 16.7 | 0.037 |
| With | 8 | 44.4 | 15 | 83.3 | |
| TOTAL | 18 | 100.0 | 18 | 100.0 | |

¹ Patient
² Percentage of patients in the group with NF (n=18)
 Logistic regression analysis

Table 16. Distribution of NF according to the presence of previous cerebral infarct (in T2) in the first MRI

| Infarct in T2 | n of NF | % ¹ | n of pt ² | Average ³ | SD ⁴ | p |
|---------------|---------|----------------|----------------------|----------------------|-----------------|-------|
| Without | 3 | 5.08 | 13 | 0.23 | 0.44 | 0.011 |
| With | 56 | 94.92 | 23 | 2.43 | 3.31 | |
| TOTAL | 59 | 100.0 | | | | |

¹ Percentage related to the complete NF group (n=59)

² Number of patients with cerebral infarct images on the initial MRI

³ NF/patient

⁴ Standard deviation

Mann-Whitney U test

Table 17. Distribution of the number of NF (after CAS) based on the presence of previous cerebral infarcts in T2 in the first MRI

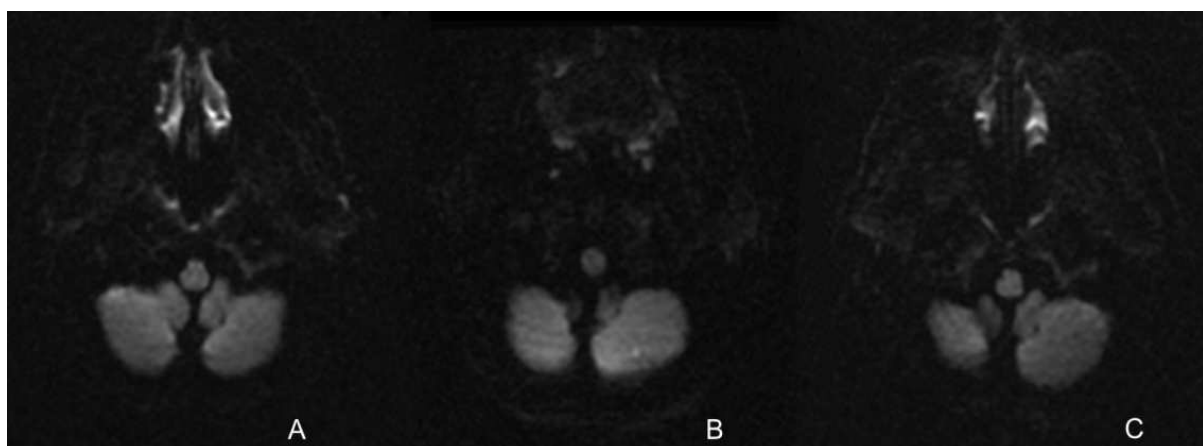


Figure 7. Patient number 19, 81 years old with bilateral stenosis in the carotid arteries. A DSA was performed in the aortic arch, common carotid arteries, left subclavian artery, and brachiocephalic trunk before the CAS of the left carotid artery. Diffusion study before the DSA and angioplasty (A). After DSA and CAS, an NF was identified in the DWI in the left hemisphere of the cerebellum (B). A new MRI performed 40 days after the CAS (not as part of the study protocol) showed the absence of lesions in the DWI (C) and in T2 (not shown).

One patient (Number 19) showed one NF in the cerebellum after angioplasty of the left carotid artery (Figure 7). Forty days later, the same patient was admitted for an angioplasty of the right carotid artery. Another MRI was performed at this opportunity (not as part of the research protocol), and it did not show diffusion lesions in the infarct area in T2 or in the enhancement, which is common for subacute cerebral infarctions.

12. Aspects of angiography and angioplasty

| NF | N | Average | P |
|-----|----|---------|-------|
| Yes | 18 | 73.83 | |
| No | 18 | 78.78 | 0.239 |

Mann-Whitney U test

Table 18. Average degree of stenosis in the groups with and without NF after CAS

| | NF | | | | p |
|--------|----|-------|-----|-------|-------|
| | No | | Yes | | |
| | N | % | N | % | |
| Ulcers | 7 | 38.89 | 7 | 38.89 | 1.000 |

Logistic regression analysis

Table 19. Presence of ulcers and appearance of NF after CAS

| NF | Occlusion of contralateral carotid artery | | | | p |
|-----|---|-------|----|-------|-------|
| | Yes | | No | | |
| | N | % | n | % | |
| Yes | 3 | 16.66 | 15 | 83.33 | |
| No | 4 | 22.22 | 14 | 77.77 | 0.674 |

Chi-squared test

Table 20. Distribution of NF according to the presence of contralateral carotid occlusion.

| NF | Total time (min) | Average (min) | SD (min) | p |
|----------------|------------------|---------------|----------|-------|
| Without (n=14) | 323 | 23.07 | 10.48 | |
| With (n=15) | 342 | 22.80 | 8.59 | 0.880 |

min: minute

Mann-Whitney U test

Table 21. Correlation of fluoroscopy time with NF after CAS

| NF | Volume (ml) | Average (ml) | SD (ml) | p |
|----------------|-------------|--------------|---------|-------|
| Without (n=16) | 2910 | 181.88 | 73.50 | |
| With (n=14) | 2570 | 183.57 | 54.01 | 0.918 |

ml: milliliter

Mann-Whitney U test

Table 22. Correlation of contrast volume used in the CAS and the appearance of NF after CAS

| Patients | n of catheters ¹ | Average ² | p |
|------------|-----------------------------|----------------------|-------|
| Without NF | 43 | 2.39 | |
| With NF | 40 | 2.22 | 0.462 |

¹ Total number of catheters used in each group

² Average catheter/patient

Mann-Whitney U test

Table 23. Number and average of catheters used in the CAS according to the presence of NF in the final MRI

| Patients | n of vessels undergoing DSA | Average ¹ | p |
|------------|-----------------------------|----------------------|-------|
| With NF | 56 | 3.11 | |
| Without NF | 50 | 2.78 | 0.628 |

¹ Vessels subjected to angiography per patient

Mann-Whitney U test

Table 24. Number and average of vessels subjected to DSA according to the presence of NF after CAS

| Arteries submitted to angiography | NF | | | | p |
|-----------------------------------|-----------|-------|------------|-------|-------|
| | No (n=18) | | Yes (n=18) | | |
| | n | % | n | % | |
| RCCA | 13 | 72.22 | 16 | 88.89 | 0.220 |
| RSUB ¹ | 4 | 22.22 | 2 | 11.11 | 0.379 |
| BAT | 6 | 33.33 | 9 | 50.00 | 0.313 |
| ARCH | 4 | 22.22 | 5 | 27.78 | 0.701 |
| LSUB ² | 8 | 44.44 | 10 | 55.56 | 0.506 |
| LCCA | 15 | 83.33 | 14 | 77.78 | 0.675 |

RCCA: right common carotid artery; LCCA: left common carotid artery; ARCH: aortic arch; RSUB: right subclavian artery; LSUB: left subclavian artery; BAT: brachiocephalic arterial trunk

¹ RSUB includes angiography of the ipsilateral vertebral artery

² LSUB includes angiography of the ipsilateral vertebral artery

Logistic regression analysis

Table 25. Number and percentage of each vessel subjected to DSA and the appearance of NF after CAS

| Type of exam (n=36) | NF | | | | p |
|---------------------|---------|------------|---------|------------|-------|
| | No | | Yes | | |
| | n of pt | % of exams | n of pt | % of exams | |
| "Brief" (n=12) | 7 | 58.33 | 5 | 41.67 | |
| "Broad" (n=24) | 11 | 45.83 | 13 | 54.17 | 0.480 |

pt: patients

Logistic regression analysis

Table 26. Type of angiographic exam used and the appearance of NF after CAS

| Technique used to access carotid | Catheterization techniques | | | | p |
|----------------------------------|----------------------------|----------------|----------------|----------------|-------|
| | Without NF | | With NF | | |
| | n ¹ | % ² | n ¹ | % ² | |
| DA | 6 | 50.00 | 6 | 50.00 | 1.000 |
| ECC | 5 | 50.00 | 5 | 50.00 | 1.000 |
| EEC | 4 | 36.37 | 7 | 63.64 | 0.283 |
| TRI | 6 | 75.00 | 2 | 25.00 | 0.124 |

DA: direct access; ECC: exchange in the common carotid artery; EEC: exchange in the external carotid artery; TRI: triaxial

¹ Number of times that each technique is used in the group with and without NF

² Percentage of access technique

Logistic regression analysis

Table 27. Correlation of catheterization techniques with NF after CAS

| Brand of stent | NF | | | | p |
|----------------|----|----------------|-----|----------------|-------|
| | No | | Yes | | |
| | n | % ¹ | n | % ¹ | |
| Precise® | 4 | 44.45 | 5 | 55.56 | |
| Protégé® | 2 | 40.00 | 3 | 60.00 | |
| Wallstent® | 12 | 54.55 | 10 | 45.45 | 0.493 |

¹ Stent/brand
Chi-squared

Table 28. Correlation of types of stent with NF after CAS

| Stent brand | n of stents with NF IP | NF IP | Average ¹ | p |
|-------------|------------------------|-------|----------------------|-------|
| Precise® | 9 | 18 | 2.00 | |
| Protégé® | 5 | 5 | 1.00 | 0.245 |
| Wallstent® | 20 | 21 | 1.05 | |

IP: ipsilateral

¹ NF IP/stent

NOTE: In this data analysis, CASs with NF outside the area where the stent was implanted were excluded.

Kruskal-Wallis test

Table 29. Correlation of stent brands with NF after CAS considering only the side where the stent was implanted

| Stent design | n of stent with NF IP | NF IP | Average ² | p |
|--------------|-----------------------|-------|----------------------|-------|
| Closed cell | 20 | 21 | 1.05 | |
| Open cell | 14 | 23 | 1.77 | 0.128 |

IP: ipsilateral

In this aggregation of the elements, CASs with NF outside the area where the stent was implanted were excluded

¹ Two patients were excluded from the analysis of laterality.

² NF IP/stent

Mann-Whitney U test

NOTE: Open-cell stent: Wallstent®; closed-cell stents: Precise® and Protégé®

Table 30. Correlation of stent designs with NF after CAS considering only the side where the stent was implanted (n=34 patients¹)

| Filter brand | NF | | | | p |
|--------------|----|-------|-----|-------|-------|
| | No | | Yes | | |
| | n | % | n | % | |
| Angioguard® | 2 | 50.00 | 2 | 50.00 | |
| Emboshield® | 2 | 28.57 | 5 | 71.43 | 0.367 |
| EPI® | 14 | 56.00 | 11 | 44.00 | |

Chi-squared test

NOTE: 100 µm pores in AngioGuard®, 110 µm in EPI FilterWire EZ®, and 140 µm in EmboShield®

In this series, there was not a case in which excess thrombus or atheroma plaque materials determined acute occlusion of the filter during the CAS.

Table 31. Occurrence of NF based on filter brand (n=36)

| Filter brand | n of uses | NF IP ² | Average ³ | p |
|--------------|-----------|--------------------|----------------------|-------|
| Angioguard® | 4 | 9 | 2.250 | |
| Emboshield® | 6 | 12 | 2.000 | |
| EPI® | 24 | 23 | 0.958 | 0.582 |

¹ Two patients were excluded from the analysis of laterality.

² NF ipsilateral

³ NFIP/filter brand

Kruskal-Wallis test

NOTE: 100 µm pores in AngioGuard®, 110 µm in EPI FilterWire EZ®, and 140 µm in EmboShield®

Table 32. Distribution of NF ipsilateral to the use of the filter, considering the different models (n=34 filters¹)

| Filter design | n of uses | NF IP ² | Average ³ | p |
|---------------|-----------|--------------------|----------------------|-------|
| Eccentric | 24 | 23 | 0.958 | |
| Concentric | 10 | 21 | 2.100 | 0.515 |

¹ Two patients were excluded from the analysis of laterality.

² NF ipsilateral

³ NF IP/filter system protection design

NOTE: Eccentric, EPI®; Concentric, Angioguard® and Emboshield®

Mann-Whitney U test

Table 33. Distribution of NF ipsilateral to the use of the filters, considering filter design (n=34 filters¹)

In summary, our DWI MRI study after CAS found that 50.00% of patients showed NF of restriction/ischemia in DWI after CAS. All of the NF were clinically silent (100%). These NF were located in a cerebral area fed by the cerebral artery subjected to CAS in 77.19% of patients and an area smaller than 10 mm in 91.53% of patients. The NF in cerebral areas not fed by the cerebral artery undergoing angioplasty corresponded to 22.81% of NFs. The presence of previous cerebral infarcts on the MRI influenced the appearance of NF ($p=0.037$).

13. Discussion

13.1. Aspects of MRI imaging before CAS

The MRI scan before CAS showed great variety in the changes in the 36 patients, with special attention to ischemic aspects. We found four (11.1%) patients with hypersignal foci (a total of six foci) in the DWI MRI before CAS. These foci are considered recent ischemia foci, and they are not reported as NF involved with CAS, although most remained after treatment. This rate is similar to that reported by Jaeger et al. [56] In a study involving 70 CAS, the authors discovered hypersignal lesions in diffusion before CAS in 10 (14%) of the patients, with a total of 24 foci [56]. Images of ischemia in DWI were detected in 10 (19%) patients before CAS by Hammer et al. [61]. Hammer et al. [61] suggested that recent ischemia foci presented by some patients on the initial MRI indicate the relevance of performing an MRI scan before CAS to guarantee that any foci in the MRI after CAS are related to the procedure.

Piñero et al. [48] found lesions in the DWI ipsilateral to the carotid artery undergoing CAS in 11% of the patients. In our data, 88.33% of the lesions found in the DWI before the CAS were ipsilateral to the carotid artery treated. This result supports the idea that these plaques are constantly forming emboli that can be sent to the brain.

Our data showed that carotid atherosclerotic plaques are probable causes of hypersignal lesions in DWI before CAS and can be considered causes of ischemia symptoms. This finding is corroborated by the fact that most patients were symptomatic (75.0%). Most of the patients (63.9%) showed old cerebral infarcts in the T2 sequence of the MRI before CAS. In our series, a strong correlation between the rates of old infarcts and positive symptoms was found (75.0%).

13.2. Diffusion MRI study after CAS

According to Bates et al. [13], while the primary purpose of revascularizing the carotid artery is preventing cerebral infarction, current treatments, both CAS and endarterectomy, carry a risk of triggering brain infarction.

All interventional procedures performed in craniofacial vascular regions carry an inherent risk of causing embolisms to the brain with different levels of severity. In these cases, the diffusion MRI technique is the most efficient tool for detecting acute focal cerebral ischemia [46,71,72].

Angioplasty is certainly the interventional procedure in the craniofacial region that carries the greatest risk of embolism. This risk is well documented in various studies and varies greatly among the different groups that it effects [35,37,73].

The institution wherein the present study was conducted published data pertaining to 1,037 carotid angioplasties with stent implantation and cerebral protection in 2006. The incidence of disabling neurological complications and death was 2.2% [38]. Despite the low morbi-mortality of the method, the real incidence of embolism is not known because the patients remained asymptomatic.

We found restriction foci in the diffusion MRIs of 18 of the 36 (50%) patients in our series. These NF in the DWI after CAS are additional to those in the first MRI, which implies that the procedure or some aspect of it is related to the appearance of NF. The fact that all of the patients in this series were asymptomatic after CAS and remained so during the intrahospital observation period should also be taken into account.

The percentage of patients with NF in DWI in similar studies is quite variable: 9 to 78% (9% [74]; 15.8% [71]; 17.3% [48]; 20.4% [75]; 29% [56]; 30% [36]; 40% [61]; 41.5% [73]; 42% [46]; 42.6% [69]; 43% [59]; 49% [34]; 52% [35], 54% [58], 59.2% [76]; 9 and 78% [77]; 70% [70]).

The comparison of different studies is very difficult because even a small variation in the period after the CAS during which DWI was conducted might affect the result. In the study by Rapp et al. [77], a total of 23 patients underwent two MRI exams after the CAS. The first MRI scan was performed immediately after the procedure (1 to 2 h) and the second exam was performed 48 h later. The results indicated only two (9%) cases with NF in the DWI immediately after the procedure and 18 (78%) cases with NF 48 h later [77]. In a recent meta-analysis that included studies that followed the evolution of CAS by DWI (1,363 CAS), NF were found in 37% of patients [37].

The study that is most similar to ours is Kastrup et al. (2006); this study found microembolia in 49% of patients with cerebral protection. Two years later, the authors updated their series and published that NF occurred after CAS with a cerebral protection filter in 52% of patients [35].

du Mesnil de Rochemont et al. [46] found NF in 42% of CAS and, similar to our study, found no neurological deficit. In addition to this study, several others [35,37,48,61,69,73] have found that most patients remained asymptomatic after CAS, despite the presence of NF. These findings encouraged us to look for factors that lead to ischemic changes.

Jaeger et al. [56] demonstrated that smaller NF are less likely to become definitive lesions. His study showed that of the 59 restriction foci in the diffusion after CAS, only 17 (29%) were observed in the T2 sequence. They found that 17% of the lesions smaller than 5 mm in the DWI were visible in T2; 36% of the lesions in DWI between 5 and 10 mm were observed in T2, and 100% of the larger lesions (larger than 10 mm) were apparent in T2 [56]. As in Tedesco et al. [70], we considered the hypersignal images in T2 as already defined and permanent ischemia foci, unlike the lesions in DWI, which may be reversible.

In a series of 59 CASs, Jaeger et al. [56] found that 75% of NF were smaller than 5 mm; in the series by Piñero [48], the lesions were smaller than 5 mm in 57% of patients. However, in a series of 22 CASs in Roh et al. [78], all of the NF were smaller than 10 mm. In our study, small NF (<10 mm) corresponded to a large majority (91.53%) of the NF, while large NF (>10 mm)

composed only 8.46% of the NF; this result shows that the eventual emboli caused by the procedure are small in size.

According to several authors, some lesions in DWI after CAS also occur in vascular regions independent from the CAS and are most likely related to the catheterization procedure [35,37,61,73]. Our data showed that most (77.19%) of the NF occurred in the region of the carotid artery that underwent angioplasty. However, a significant difference was not observed between the side of the CAS and the contralateral side in relation to NF.

In the publication by Piñero et al. [48], 67.9% of the NF were in the vascular area compatible with the CAS. However, Hammer et al. [61] found a similar number by studying 53 carotid angioplasties: 60% of the NF were in an ipsilateral situation to CAS and 40% occurred in contralateral topography.

By studying carotid angioplasty, Poppert et al. [58] found NF in DWI in area of contralateral carotid or vertebral artery in 9.7% of patients. Poppert et al. [58] stated that during catheterization, to reach the right internal carotid artery, the materials must pass the aortic arch at the origin of other cerebral arterial trunks, such as the common carotid artery and left subclavian artery, in addition to the brachiocephalic trunk next to the right vertebral artery. Thus, material from plaques along this route can cause emboli in various brain regions beyond the area nourished by the carotid artery undergoing CAS [58].

Maleux et al. [73] described their surprise at finding that 35.3% of the NF (26.3% in contralateral anterior circulation and 9% in the cerebellum) occurred in regions not nourished by the carotid artery ipsilateral to the CAS. They considered the manipulation of the guide wire, catheter, or guide catheter in the aortic arch as a possible cause of the lesions [73].

A meta-analysis with data collected from CAS studies between 2000 and 2007 found lesions in diffusion in 14.5% of CAS outside the region treated, and NF were observed in 35% of the procedures in the region of the carotid artery treated by CAS [37]. Thus, catheterization was one of the main causes of the microemboli.

In our study, half of the patients with NF had a single lesion (single NF), and the other half showed multiple foci (varying from 2 to 11 NF), which totaled 50 NF. Thus, patients with multiple NF accounted for 84.75% of the NFs found in diffusion. Our study reproduced the finding of Piñero et al. [48]. These studies found a single focus in DWI in 53.6% of patients, and multiple foci were found in 46.4% of the patients in diffusion after CAS [48].

In our study, we found five patients who showed ipsilateral NF, five patients who showed contralateral NF, and another six who showed ipsilateral and contralateral NF simultaneously. Thus, the ipsilateral situation was the main localization of the NF occurrence in absolute terms, but the most common presentation was associated to the contralateral NF than isolated. A similar distribution of laterality was found in a retrospective study by Tedesco et al. [70] of 27 CAS. Similar numbers were also observed by Hammer et al. [61], who, in a series of CAS under cerebral protection, found eight cases with only ipsilateral NF, seven cases with exclusively contralateral NF, and six cases with a combination of ipsilateral and contralateral NF. According to these authors, these events can be related to the doctor's skill in catheterizing the aortic

arch and the supra-aortic trunks and to the prevention of emboli formation beyond the collateral circulation by the Willis polygon or other routes [61].

When patients with NF in an area other than the carotid artery for angioplasty are excluded (i.e., emboli resulting from catheterization), our risk of cerebral embolism from angioplasty alone is reduced from 50.00% (18 patients) to 32.35% (11 patients).

du Mesnil de Rochemont et al. [46] found an average of one NF per patient in the ipsilateral area, while Jaeger et al. found that the average number of NF ipsilateral to the CAS was 2.6 per patient and that the average number of NF contralateral to the CAS was 1.2 per patient [56]. In our study, the average number of ipsilateral NF was 2.8 per patient, and the average number of contralateral NF was 1.0 per patient.

The highest mean (6.33) NF per patient was for the presentation of ipsilateral and contralateral NF simultaneously. This finding justifies the idea that the initial angiography or the catheterization technique and the CAS are involved in the high average number of bilateral NF.

Our average number of NF per patient, which was higher than that reported by most authors, may reflect the fact that most (66.7%) of our cases underwent a broad diagnostic exam before the angioplasty. Thus, the hypothesis can be applied that, because most of the cases had bilateral NF, these NF were more likely related to the catheterization than to the angioplasty itself.

Because of the risk of embolism during angiographic exams (diagnostic) and in interventional procedures such as CAS, we believe that the exams should be performed by certified and experienced neuroradiologists only. This statement is supported by other authors [71,79].

Moreover, modern noninvasive methods can be used with good reproducibility in some centers, allowing a definition of the anatomy, degree of stenosis, and intracranial circulation, which enables decisions about the CAS to be made without the use of a broad angiography before the CAS.

Several other authors [8,48,56,58,71,80-82] studied risk factors for the occurrence of atherosclerotic disease and ICVA, including diabetes, hypertension, coronary artery disease, ischemic peripheral vascular disease, hypercholesterolemia, arrhythmia, previous ischemic stroke, previous TIA, vasculitis, and hemorrhagic cerebrovascular accident. Most authors did not find significant differences related to the appearance of hypersignal foci in DWI. Some authors found some relevant factors, but those were not confirmed by other authors.

Clinical risk factors were not significant determinants of the formation of NF after CAS in our study. The only risk factor statistically proven to be involved in the creation of lesions in DWI after CAS was a radiological factor: old cerebral infarcts shown on MRI images, especially in T2W.

Our study found a tendency toward a greater number of NF in older patients (≥ 75 years) and those who underwent angioplasty of the left carotid artery. Hammer et al. [61] identified a tendency for NF to be found in patients with advanced age (> 75 years); however, as in our study, they failed to prove it statistically ($p=0.1$).

du Mesnil de Rochemont et al. [46] confirmed this trend by finding that age above 70 years old was a predictor for the occurrence of foci in diffusion, and they wondered whether this finding could be related to the fact that more elderly patients have more diffuse atherosclerosis compared with younger patients. These authors did not find a significant correlation for factors such as gender, degree of stenosis, type of stent, type of filter, and risk factors, such as hypertension, diabetes, smoking, hypercholesterolemia, coronary heart disease, and peripheral arterial occlusive disease [46].

Generally, our group without NF showed fewer risk factors (56 factors) than the group with NF after CAS did (60 factors). While not significant, the difference shows a tendency that the more comorbidities the patient has, the greater his or her risk of developing NF in a CAS. The difference was also not significant for the clinical conditions of previous ischemic cerebrovascular accident and transient ischemia attack. Similarly, for the risk factor of cerebral ischemia, which was associated with both TIA and ICVA, the difference was also not significant.

In our group (n=36), which was characterized by advanced age (average of 72 years), serious stenosis (average narrowing of 76.31%) and symptoms of previous ischemic conditions in most patients (72.22%), the subgroup of previously asymptomatic patients showed a lower risk of NF: only 18.6% of the observed NF. Moreover, a large majority, 48/59 (81.4%) of the NF occurred in symptomatic patients. Despite this tendency, there was not a significant difference. Hammer et al. [61], in a series of 53 CAS, identified a tendency to find NF in symptomatic patients, although no statistical proof was found.

According to Kastrup et al. [35], it is conceivable that the high prevalence of active plaques with thrombotic activity in recently symptomatic patients may determine the high rate of NF in this group. When our patients are regrouped into asymptomatic (9 patients) and symptomatic (27 patients) groups to evaluate the interference of previous symptoms with the occurrence of NF, the hypothesis is confirmed. The asymptomatic patients did not develop NF in most (77.8%) of the CAS cases, while the symptomatic patients showed NF in most cases (59.3%). Again, the analysis did not prove a significant difference ($p=0.121$), but it confirms the tendency for symptomatic patients to be at greater risk in the procedure. Piñero et al. [48] also showed an increased risk of embolism in angioplasty for symptomatic patients in their series (19.8%) compared to asymptomatic patients (10%; $p = 0.155$). This ratio is approximately 2:1, while ours was approximately 2.7:1.

We found a significant difference in the NF lesions in DWI after CAS in patients with previous infarcts (based on the T2 sequence) compared with those without. Cerebral infarct was present in 63.9% of patients in our entire series. It was observed that most (83.3%) of the patients with NF after CAS showed cerebral infarcts on the MRI before the CAS. Nonetheless, the patients who did not show cerebral infarcts on the MRI before the CAS mostly evolved (55.6%) without NF in the DWI after CAS ($p=0.037$). Again, the average number of NF varies enormously in relation to whether the patient had or not a previous infarct on T2 (initial MRI). The average NF in the group with a previous cerebral infarct was 2.43 NF/patient, while the average in the group without a previous infarct was only 0.23 NF/patient ($p=0.011$).

This association makes it clear that a definitive ischemic lesion in imaging (in T2W) is a great risk factor for developing microembolic complications during carotid angioplasty. Thus, the patients who have infarcts caused by embolism or other factors are the same patients who present NF after CAS. Additionally, the tendency for symptomatic patients (who do not necessarily always present infarcts on MRI) to exhibit more NF after CAS indicates that the main cause of microemboli during CAS may be the patients' condition, including the plaque composition, risk factors, and how the atherosclerosis presents in their bodies. It is possible that the NF are signs of the underlying disease, and they may be exacerbated during CAS. Our idea about the vulnerability of plaque is shared by Piñero et al. [71], who evaluated the composition of the material found in the filters after CAS and stated that the atheromatous plaque and the vessel wall are the main sources of microemboli during CAS.

Despite several publications on signs compatible with microemboli after CAS and CEA, no consensus can be found among authors regarding the real clinical representation of NF. According to some authors [62,69], the clinical value of NF after CAS is not adequately clear. In our study, although 50% of patients showed foci compatible with ischemia in the diffusion after angioplasty, none showed ischemic neurological syndrome. Some published series have obtained a similar result, meaning most patients with NF after CAS were asymptomatic [46,54].

While the brain shows some tolerance for microemboli [83,84], the fact that subclinical deficits promoted in the NF areas after CAS may cause long-term neurological deterioration cannot be neglected. Long-term studies on cognitive function are needed.

The clinical impact of these clinically "silent" lesions in the brain that do not cause motor, sensory, or linguistic deficits (i.e., in non-eloquent brain areas) was debated by Bendszus [63, 80]. According to these authors, there is evidence that the cumulative load of ischemic brain injury can cause neuropsychological deficits or aggravate vascular dementia.

However, the discrepancy between the clinical safety of CAS and the number of NF of ischemia is intriguing. It is known that there can be TIA abnormalities in DWI that undergo regression and do not cause lesions that remain as ischemic scars in T2. Despite the normalization of DWI after TIA, structural damage caused by late neuronal apoptosis may be present, even in the absence of tissue necrosis [63]. For these authors, DWI shows the entire picture of emboli during different procedures, and the ischemic conditions are only the visible tip of the iceberg [63].

Studying the DWI sequence in patients with clinical conditions of TIA, Kidwell et al. showed that in five of nine patients with ischemia foci in DWI after TIA, no evidence of infarcts was found in follow-up imaging scans, indicating that almost half of the lesions from DWI in TIA may be completely reversible on imaging [85]. Thus, we most likely overestimate the true incidence of cerebral ischemic lesion after CAS when we base it only on DWI of MRI.

Although not part of research protocol, an MRI scan was conducted 40 days after CAS in a patient who showed NF in the MRI after CAS. The third MRI scan did not show ischemic lesions in the DWI or in T2. Thus, the NF indicated in the MRI after CAS proved evanescent (like short-lived). This suggests that small lesions in the DWI that occur after CAS and are clinically silent may not be definitive ischemic lesions.

Similarly, a small study (seven patients) from Schlüter et al. [86] identified reversal on imaging in 76% (5/21) of the NF after CAS at an average MRI follow-up four months later. A recent study showed that 92.1% of the signs of microemboli disappeared and that 5.2% remained in an MRI study three months after the CAS [72]. Thus, the NF after CAS are potentially reversible on imaging and without neurological developments [60,75,86].

Some authors [69,87] correlated the neurological deficits after CAS with the diameter of the foci of ischemia in the DWI. Small lesions were associated with good clinical evaluation. Small NF (>5 mm) were reported as having the highest chance of not becoming definitive ischemic lesions in later MRI scans compared with NF larger than 5 mm [75]. In addition to the size of the foci in DWI, the topography may also determine whether the lesion will be clinically silent or not [56,71].

For Piñero et al. [48], the position of the lesions in the diffusion was predominantly cortical and subcortical in 67.9%. The study by Jaeger et al. showed that 95% of the NF had a cortical/subcortical localization, mainly in the area of the ACA and MCA. Jaeger et al. considered this distribution to be more compatible with standard cerebral embolism than with types of cerebral ischemia [56].

Similar to Piñero et al. [48] and Jaeger et al. [56], the predominant pattern of the NF in our study were lesions with small diameters and apparently random distribution. This finding is compatible with the topography of the distal arteries, including the cortical and subcortical vessels and perforating branches. There was also no predominance in border (“watershed”) areas of vascularization.

Although we found NF in various areas, such as the motor cortex and basal ganglia, the patients presented no clinical deficit during the hospitalization period. It may be that because the NF had a small volume, they were less relevant for clinical lesions due to collateral circulation, despite being in eloquent area. Nonetheless, improvement in cerebral perfusion was shown after CAS in publications by Tavares and Caldas and may counterbalance clinical damage resulting from microemboli that occur after CAS [68,88,89].

13.3. Aspects of angiography, angioplasty, and cerebral protection

In addition to maintaining a constant flow to the brain in all phases of CAS, cerebral protection with a filter is likely to be used in all cases (unlike the occlusive balloon technique, which is reserved for patients who are candidates for temporary carotid occlusion) [42]. Other limitations of techniques that use balloon for cerebral protection include severe tortuosity of the cervical and thoracic arteries and increased diameter of the external carotid >6 mm [72]. These were our reasons for choosing filters as a means of protection in our cases.

Angiographic factors and factors in the angioplasty, such as percentage of stenosis, presence of ulceration in the plaque, and number of catheters used, did not show a statistically significant difference in our study with respect to the appearance of NF after CAS. In contrast to our findings, Ohki et al., studying ex vivo angioplasty with stent, found that the greatest number of particles during the procedure was associated with serious stenosis >90% [90]. Gauvrit et al. [74], similar to our findings, did not find a significant difference between the degree of

stenosis in groups of patients with and without NF after CAS. Schnaudigel et al. [37], in a meta-analysis, considered that the degree of stenosis influenced the incidence of NF after CAS; however, it was difficult to compare the articles because of great variation in the diagnostic methods (DSA, CTA, MRA, and Doppler) and methodologies (NASCET, ECST or not mentioned) used to grade the stenosis [37]. Roh et al. [78] found NF after CAS in eight of 22 (36%) cases. Thus, similar to us, they did not find a significant difference in the presence of NF in relation to the presence or absence of ulcers in the plaque. Among our patients, the percentages with ulcers were identical in the groups with and without embolism in CAS.

We note that ulcers did not influence the result of embolism, although one of the steps, overcoming the ulcerated stenosis by the still-closed closed filter, occurred without cerebral protection. This fact may suggest the safety of filters in crossing stenotic lesions, even anatomically complex ones, such as ulcerated plaques. More studies are needed to prove this hypothesis. Lacroix et al. [69], in a series of 61 CASs, analyzed technical conditions such as the procedure duration and presence of ulcers in atheromatous plaque. They did not find a correlation between these elements and the frequency of NF in DWI.

We did not find a significant difference between contralateral occlusion and the occurrence of NF after CAS. This finding confirms the clinical reasoning that patients with carotid stenosis and contralateral carotid occlusion have an embolism risk similar to that of other patients during CAS treatment. This fact contrasts with endarterectomy, for which the clinical results are materially negatively influenced by the presence of contralateral carotid occlusion [10,91-93].

The fluoroscopy time used in CAS may reflect the technical difficulty of the procedure as this time is equivalent to the set of short intervals in which X-ray was applied during the maneuvers necessary for the catheters, guides, balloons, stents, and other materials [82]. Pinheiro et al. [48] used fluoroscopy for 21 min (average) per CAS, a result similar to our series (22.93 min per CAS). As in our study, Tedesco et al. [70] did not find a correlation between long fluoroscopy times or greater amounts of contrast and the appearance of NF after CAS. Conversely, Rapp et al. [77] found an increase in NF after CAS depending on the fluoroscopy time used. However, the fact that we did not find a significant difference in the fluoroscopy time between the groups with and without embolism suggests that cases in which the angioplasty is technically difficult may require longer times for the interventionist, but theoretically, the increased time does not increase in the risks of embolism. The CASs in this study were always conducted by an individual with a considerable amount of experience. The only way to exclude this bias would be to evaluate the learning curve of a technician in training, which may explain the results of [77].

Although each contrast injection has an unknown theoretical risk of carrying emboligenic particles, this was not proven in our series, but there was not a significant difference in volume between the groups with and without NF. Nonetheless, we remember that, in medical services such as ours with a neuroradiology practice, the cases of embolism are possibly not due to the technique used because the contrast volume and the fluoroscopy time are similar for both groups. Moreover, it is possible that the risk of embolism may be endogenous to patients at a neuroradiology institution where the iatrogenic embolism factor is studied and controlled. The

study by Kato et al. [94], as well as ours, did not find a significant difference in the groups with and without NF regarding contrast volume, duration of the procedure, and the use of additional catheters.

In our series, greater number of angiographies was found in the group that showed NF, and the occurrence of NF varied based on the type of exam applied. Most of the exams defined as broad were associated with emboli, and most of the brief exams did not show any NF after CAS. However, there was no statistical confirmation.

Following the same trend, the average DSA per patient was greater in the patients with NF (average 3.11) than among patients (average 2.78) without NF. Despite the theoretical risk of increasing embolism with the diagnostic exam, the statistical analysis was not sufficient to prove this hypothesis. Thus, the greater the number of vessels on which angiographies were performed, the higher the occurrence of NF. The logical deduction is that conventional angiography has the same responsibility for causing NF as angioplasty alone.

The catheter itself is a potential source of embolism, although complication rates are low [95], and most complications are asymptomatic ischemic complications [61]. Bendszus et al. were the first to publish diffusion MRI as a detection method for clinically silent emboli after cerebral angiographies. They found 42 hypersignal foci in the DWI in 23 out of 100 (23%) patients after DSA with manual injection of the contrast, all without neurological deficits [80].

Britt et al., in a short series, estimated an incidence of less than 9% of asymptomatic cerebral infarcts in diffusion in patients undergoing cerebral angiography for diagnostic purposes [96]. Kato et al. [94], in a study of 50 patients, observed NF in the diffusion after DSA in 8 of the 41 (19.51%) patients. Chuah et al. [97] found NF after angiographies in 3 of 20 (15%) patients, all of which were smaller than 10 mm and occurred at a rate of only one per patient.

Angiography of the aortic arch before CAS was associated with a high risk of microemboli, according to a publication of 27 CASs by Tedesco et al. [70]. This study reports that the aortography by catheter was avoided in cases where ulcers or stenosis were identified in the aortic arch during the revision of exams conducted immediately before CAS. Some authors have reduced the use of aortography by catheter. After the inclusion of MRI angiography in the protocol by Rapp et al. [77], digital angiography by catheter was abolished in 81% of CASs.

In the detailed statistical analysis using logistic regression of our data, we did not find a significant difference between DSA of the aortic arch ($p = 0.701$) and the appearance of NF in diffusion after CAS. In addition to CAS and DSA, several other catheter techniques show risks of cerebral embolism during the procedure. Rordorf et al. [98] found lesions in diffusion in 8 of 14 (57%) patients after embolization of unruptured cerebral aneurysms. In this series, the majority, with the exception of one new focus, was ipsilateral to the treated aneurysm [98]. Cronqvist et al. [99] published a series of 21 patients suffering from cerebral arteriovenous malformation who underwent 50 embolization procedures. In their study, NF were less frequent (22% of procedures). Of the 35 NF found in DWI, 23 (66%) were of ischemic origin, 8 (23%) represented perinidal venous clots, and 4 (11%) were of uncertain origin [99].

Brain catheterization is not the only cause of brain embolism. In prospective studies, there was an incidence of up to 15% for cerebral NF after cardiac catheterization [100]. Ischemia foci in

DWI are found in a substantial number of carotid surgeries (endarterectomy), heart and coronary surgeries, and interventions with cerebral angiographies [63,101,102]. Cardiac bypass surgery may induce NF for cerebral ischemia in up to 45% of patients [103].

Willinsky et al. [82] point to mechanisms related to brain catheterization, such as thromboembolism resulting from the withdrawal of the guide within the catheter. The withdrawal causes the empty space of the catheter to fill with blood. This space is subjected to stagnation, unnoticed by the inexperienced practitioner, and causes the formation of emboli [79]. Other mechanisms cited are the dissection and fracture of plaques; the fragmentation of plaques with catheters, guide catheters and guide wires; platelet activation; changes in clotting factors; and the introduction of air bubbles [36,46].

Willinsky et al. [82] published a five-year retrospective study of 2,899 cerebral angiographies and found neurological complications in 39 (1.3%), 20 of which were transitory (0.7%), five (0.2%) were reversed, and 14 (0.5%) were permanent. Neurological events in angiography were significantly more frequent in older patients (>55 years) and patients with concomitant cardiovascular disease and when the fluoroscopy was longer [82]. Kaufmann et al. [95] published the widest series of cerebral angiographies that resulted in clinical complications by evaluating 19,827 consecutive patients in a 22-year retrospective study at the Mayo Clinic. They found neurological complications in 2.63% of patients, permanent infarcts in 0.14%, and deaths in 0.06% [95]. Hematoma at the puncture site was the most common occurrence (4.2%). The independent factors identified as associated with neurological complications included atherosclerotic cerebrovascular disease, transient ischemic attacks, and subarachnoid hemorrhage [95].

Therefore, we assume that there is a theoretical risk of brain embolism, including possible severe ischemic events, with all of the interventional procedures.

According to some authors, the diffusion MRI technique is the most efficient tool for detecting acute focal brain ischemia [68,71,76].

Among the interventional procedures, carotid angioplasty achieved a significant reduction in embolism with the introduction of protection systems, but emboli were not avoided completely [35,37,46,68,73]. Good practice in neuroradiology procedures appears to be a mitigating factor for embolic damage during carotid angioplasty procedures. Consistent with our idea, Verzini et al. and Piñero et al. said that the interventionist's experience is a factor for reducing periprocedural complications [68,71,104]. For du Mesnil de Rochemont et al. [46], unintentional movement of the filter during the intervention is a potential cause of microemboli and mainly occurs during the initial learning curve. This movement can largely be avoided with improved interventional technique and new materials [46,68]. We believe that the learning curve for CAS might be long and could exceed 200 cases.

Tedesco et al. [70] stated that their CAS program was modified to include the omission of the aortic arch. This change began when MRI images provided sufficient anatomic detail and initiated anticoagulation before the passage of guides and catheters in the ascending and transverse aorta [70]. Thus, these authors state that aortography should be reserved for patients for whom the MRI before CAS does not provide anatomic details to guide the catheter. In

contrast, these same authors affirm that more complex and challenging aortic arches (described as Type II and Type III) were not identified as high risk for embolization [70]. Most authors describe rates of non-symptomatic NF in DWI in the area contralateral to CAS that are similar to brain angiography rates.

The initial catheterization of CAS cannot be excluded because the procedures cannot be separated. Although the catheterization occurs alone for diagnostic purposes [80], angiography is a mandatory initial stage for all angioplasties [36]. Bendszus et al. [105] subsequently published that the use of heparin and air filters materially reduced ischemic events in brain catheterization.

Most studies on the relationship between NF in DWI and CAS only mention the material used; few describe a single access technique for the common carotid artery, usually direct access. In all cases, we used a standardized form for the highest-caliber (8 Fr) guide catheter, believing that the good stabilization of the system achieved by this material facilitates the manipulation of materials (filter, stent, balloons).

In our experience, direct access without exchanges is preferable only in technically simple cases with favorable anatomy. According to our review, our study is the only one that comparatively analyzes the catheterization access technique with the guide catheter in the carotid artery undergoing angioplasty. The risk for each technique to be involved with embolism was 50.00%, 50.00%, 63.64%, and 25.00%, respectively, for direct access, exchange in the external carotid artery, exchange in the common carotid artery, and triaxial. Thus, the triaxial technique showed a tendency for greater safety, possibly by having a more gradual progression of size (from the guide wire to the guide catheter) and causing less aggravation of the aortic arch and supra-aortic trunks. We can add that the triaxial technique should be used as a first attempt when technically possible.

Because the triaxial form of access showed a small number of NF, although without statistical significance, it is possible to predict that replacing the set (a short-valved introducer and guide catheter) with a long sheath (110 cm), which is currently available, in a single product that is also used triaxially (introducer, sheath, and guide) may reduce the index of embolic complications. More comparative studies of compatible techniques (guide, catheter, sheath) and other techniques are needed to prove this trend.

Although the filter is the central focus of discussion in most articles cited here for preventing embolization during CAS, the stent is the material used to effectively treat plaque to prevent embolic ischemic conditions in the long run. Our data do not show important significant differences between the brands of stent tested and the brands of protection filters used, as in Kastrup et al. [35] and Palombo et al. [75]. However, it is possible to identify a tendency for a smaller number of NF with a closed-cell stent (Wallstent®) compared with the open-cell stents. The Protégé® stent showed a reasonable resolve for the appearance of NF ipsilateral to CAS, but the small number of times this material was used precludes reliable statements about this relationship.

Schillinger et al. [30], studying the impact of open-cell versus closed-cell stents, reviewed data from 10 European centers totaling 1,684 patients and did not identify a significant difference

regarding neurological complications and death up to 30 days after CAS. Additionally, du Mesnil de Rochemont et al. [46] found a tendency for a greater number of ischemic lesions with the use of segmented nitinol stents (open cells) compared to Wallstent®. They suggested that open-cell stents are used in more technically complex cases with marked vascular tortuosity. In our study, we obtained the same result, but the types of stents were used without differentiation regarding tortuosity. A prospective study by Sahin et al. analyzing patients with closed-cell and open-cell stents showed that open-cell stents were less associated with clinical events of brain ischemia [106]. Moreover, Hart et al. [45], studying 701 CASs, stated that closed-cell stents and eccentric filters had lower rates of TIA/ICVA/death combination 30 days after the procedure in symptomatic patients and patients with echolucent plaques in ultrasound. Our results and from other authors led to the theory that these stent and filter designs may be intrinsically more effective at preventing brain embolism from fractured plaque or other thrombogenic material.

The retrospective analysis of 3,179 consecutive CASs by Bosiers et al. [107] showed a significant difference with a greater rate of neurological complications (symptomatic or not) with open-cell stents. Using DWI specifically to study NF after CAS, the recent meta-analysis from Schnaudigel et al. [37] shows that the incidence of NF after CAS was significantly greater in open-cell stents than in closed-cell stents. Thus, our study is in agreement with those of other authors [32,37] and supports the idea that closed-cell stents are sufficient to cover plaque and prevent the embolization of large plaque particles post-CAS through the struts of the stent.

Several studies with separated groups with and without cerebral protection support the effectiveness of protection systems [34,35,37]. Kastrup et al. [33] found a combined frequency of CVA and death after 30 days of 1.8% for the group with protection and 5.5% for the group without protection ($p < 0.001$). Additionally, a lower incidence of serious neurological complications was found when a filter was used (2.2%) than without a filter (5.5%) [38]. By studying groups with and without protection and the relationship with NF formation, Kastrup et al. found emboli in 49% of patients with cerebral protection and 67% of patients without protection [34]. Two years later, this group updated their data and published the occurrence of NF after CAS without a filter in 68% of patients and 52% of patients with a filter [35].

As expected, the meta-analysis by Schnaudigel et al. [37] found a lower index of foci ipsilateral to the CAS in DWI in patients with the use of cerebral protection systems (33%) than in patients without the use of protection (45%). The same authors cited no change in the risk of NF occurrence in the contralateral area with or without cerebral protection (respectively, 14% and 13%; $p = 0.6$) [37]. In our study, all cases were performed with a protection filter. The use of a control group without a filter would be considered unethical according to our research group. However, different types of filters were compared, and the technique used to place the guide catheter was analyzed.

In addition to innovation of materials, proper training is needed for each type of filter. Attention to the correct apposition of the filter device should be a mandatory stage in the CAS [108], as it requires experience in executing the procedure because of the natural tortuosity of carotids. Positioning can be hampered by vascular tortuosity, which is sometimes excessive.

The choice of filter is also important because, if it has a smaller diameter than the vessel, blood and particles pass between the filter and the artery wall [46,104,109].

Two articles from Müller-Hulsbeck et al. [47,57] using an animal model of the carotid artery showed that miniscule particles of debris smaller than 100 μm can pass the pores of the filters [57]. Additionally, the filters can damage the vessel walls [47], which may subsequently result in the displacement of fragments and thrombi due to accidental movement of the filtering device. Other authors claim that we cannot exclude the possibility that when the filters are closed and removed, the collection system may swing the tool and loosen some of the captured particles, freeing them in the vessel lumen [46,68].

It is possible that because the stent and balloon use a microguide for the devices, in the case of the EPI/EZ® and Angioguard® filters used in this study, they may mobilize the filter and release free particles. The Emboshield® device does not carry this theoretical risk because it stays no fixed to the guide while it is in action. However, in our study, the Emboshield® device has an average appearance of NF similar to the other concentric device, Angioguard®, and both have a higher average than the eccentric device EPI®. This result reflects the need for training with each device because the only way of preventing the displacement of materials is the correct use of the devices.

In 2000, Coggia et al. [110] published the passage of particles in all stages of CAS in an ex vivo study. Most of the particles were smaller than 60 μm , and the pores of the commercially available filters were approximately 100 μm . The passage of these particles through the protection devices and entrapment in capillaries or cerebral arteries is possible [110]. Angelini et al. [50] showed through electronic microscopy that 83.7% of filters have particles adhered to them and, on average, the filters contained 33.7 particles (24 to 46). In that study, the average diameter of the fragments captured in the filters was 289.5 μm (1.08 to 5043.5 μm). The main particles found by this group were soft acellular material, lipid-laden macrophages, and cholesterol clefts. Less frequently, they found calcium particles and platelet aggregates. All of these materials are typically identified in atherosclerotic plaques, whether they are complicated or not. When a protective balloon was used, similar materials were found [50].

In 2009, Piñero et al. [111] published a structural analysis of the material contained in filters after angioplasties and stated that atherosclerotic plaques and vessel walls are the main sources of microemboli during CAS [71,111]. However, a study on the action of cerebral protection devices found that 88% of particles were retained in the filters in an ex vivo simulation of CAS [112]. Piñero et al. [48,71,111] considered filter diameter to be very important but not the only factor in the formation of NF. They claimed that bad positioning of the filter on the carotid wall due to tortuosity, displacement of the filter while handling the materials, and high profile crossover are technical difficulties that await future studies and improvements in materials. Rough handling can promote the formation of emboli during the positioning and removal of the filter.

Some authors explain that the size of debris removed from the filters differs from the real size at the moment of embolization and that most of the small emboli may be the result of the fragmentation of particles trying to pass through the grid of the filter [113]. Thus, continuous

flow predisposes the fragmentation of content retained in the filter. Physician experience and speed are necessary to reduce the time of the procedure and avoid this fragmentation and potential emboli between the pores [68].

The filters that were used in the protocol of this study had mesh with pores from 100 to 140 μm , reducing the migration of cholesterol crystals and clots, platelet aggregations, and macrofragments of atheromatous plaques through filtering. The diameter of the filter pores used was smaller than the particles described by Theron et al. [114] and Ohki et al. [90] and than most of the particles described by Angelini et al. [50].

Our series showed an average of 1.6 NF per patient, a number well below the average of 33 particles found adhered to filters in the study by Angelini et al. [50]. It is possible that filters provide real protection, given the disparity between these numbers. Nonetheless, the action of each individual's thrombolysis system cannot be excluded as also drastically, or at least partially, reducing the permanence of emboli at its distal point.

The disparity between the low number of ischemic events after CAS [33,38] and the relatively high frequency of multiple small restriction foci in diffusion after CAS [35,69,70,73] that are compatible with embolism suggests that filters mainly act by retaining large particles that could evolve into clinical conditions of ischemia, rather than by grasping small particles. In our series, the eccentric filter EPI® had embolism in diffusion in 44% of cases, suggesting apparently superior protection compared to other models. The Angioguard® filter contained emboli in 50% of cases, while the Emboshield® device showed the highest rate of emboli (71.43%) in the group. Our data establish a strong tendency for superior protection measured in the eccentric filter (0.958 NF ipsilateral) compared to the concentric designs (2.100 NF ipsilateral). A study from Tedesco et al. [70] found a high rate of NF (70% of patients). These authors used a combination of the concentric filter and the open-cell stent, which may have contributed to the high rate of emboli. While there may be unequal protection between these filters, the difference shown in this series is not statistically significant. Our data cannot completely indicate greater protection of the eccentric model compared to the concentric model. Furthermore, poor distribution among types of filters with very small groups (Angioguard®, n=4) was observed. Thus, we avoid speculative comparison regarding the safety of each device.

A retrospective study of 3,160 CAS published Iyer et al. [115] found that the type of protection (nine different systems, including concentric and eccentric filters and proximal and distal occlusion balloons) had no influence on the clinical result. However, these authors did not study the brain using MRI after CAS.

For Piñero et al. [48,111], the difficulty of correctly positioning the filter on the wall of tortuous vessels, the displacement of material during the release, the creation of emboli by the relatively high-profile crossover and low flexibility, the loss of accumulated particles during the removal of the filter, and the diameter of the filter's pores appear to be very important to the appearance of ischemia related to embolization. This finding should lead to future studies that help to perfect protection systems [48,111].

In 2006, du Mesnil de Rochemont et al. [46] found three (6%) occlusions of filters by debris or clots in a series of 50 CASs. In a series of 162 CASs, Piñero et al. found filter occlusion in four (2.5%) patients during the procedure [48]. It is predicted that these cases will become significant infarcts due to the large size of the particles because it was sufficient to obstruct the filter pores up to total occlusion of the flow. Piñero et al. [48] assume that, without the use of a filter in these cases, the morbidity of their series would increase from 4 to 6.5%.

There was no case of filter occlusion by debris or thrombi in our series. Vasospasms related to the filtering devices were short-lived and without hemodynamic impairment. Other complications related to the filters were not found in this series. Filter occlusion leading to a stopped flow is a rare occurrence. It was more observed with the use of the first generation of EPI® filters, where the diameters of the pores were only 80 μm [46,116].

While the first step in CAS, which includes catheterization, the positioning of the guide catheter and the passage of the filter over the stenosis, occurs without protection, the phases with the greatest number of emboli released from plaque are the implantation of the stent and the angioplasty by balloon. An overload of the filter protection system is the angioplasty by balloon. Piñero et al. [111] showed that the more balloon dilations are applied to CAS, the greater the load of emboli found in the filters. Therefore, physician experience is necessary to use the balloon as delicately as possible.

Unfortunately, the other technique currently used in the treatment of carotid stenosis – CEA – also has ischemic complications [59] and more brain emboli than CAS [37,83]. Another common complication in CEA is lesions to the cranial nerves and cardiac infarction [117,118].

Comparative studies between CEA and CAS found a greater number of NF after CAS than after CEA. However, the lesions in the DWI after CAS are significantly smaller than after the endarterectomy. Analyzing the NF in the DWI after CAS and endarterectomy, Roh et al. [78] reasoned that the lesions in diffusion after CAS are generally asymptomatic and that the lesions in DWI associated with symptoms are more frequent in CEA [37,78]. In recent years, the materials used in CAS have been improved to reduce complications. DWI can be used as a tool in this evolving analysis of materials and also in the technical improvement of neurointervention.

Our study shows some limitations. Data collection of a control group without the use of cerebral protection to prove the device's effectiveness is incorrect based on our ethical views of the procedure, but it is a limitation of the study. However, other published studies that conducted CAS with and without protection systems clearly show a smaller number of NF [35,37] and lower risk of ischemic events [33,38] after CAS in the groups where the devices were used.

The formation of emboli can be impeded by antiplatelet and anticoagulant medications [76], but this is not the focus of our research shown here. In neuroradiology procedures, the prevalence of resistance to aspirin varied from 2 to 21%, and resistance to clopidogrel varied from 43 to 52% [119-121]. This result is extremely important because atheromatous plaques and superimposed thrombi are the main source of microemboli during CAS. A recent study from Song et al. [76] using the VerifyNow system showed that the frequency of resistance to

clopidogrel was significantly higher in patients with foci of microemboli in DWI after CAS than in patients without foci of microemboli in MRI after CAS. In their series, all the patients who showed clinical ischemic events had resistance to antiplatelets [76].

A randomized prospective study evaluated platelet activation after coronary stents in pigs and showed that the closed-cell stent produced less intimal prolapse and thus a smoother stent-vessel wall interface than the stent with open-cells and that platelet activation was greater during the 30 days following implantation of an open-cell versus a closed-cell stent [122].

Our study concentrates on the designs of stents and filters, but other particularities of constructing the materials can interfere in the safety of CAS, such as the type of filtering element. A study considered that perforated membrane filters have greater resistance to cerebral blood flow [123], but it did not evaluate whether there was greater capture of emboli. Our study also had a relatively short follow-up time. We only used the period when the patients were hospitalized, generally three to four days. We consider that this peri-procedure period is sufficient to evaluate the late appearance of NF because the disappearance of NF is described in some cases [60,68,75].

14. Conclusions

The use of protection systems aims to avoid massive embolism, which occasionally happens. However, a perfect cerebral protection system is not commercially available. While cerebral protection with filters is effective, it is necessary to develop new protection devices that are more effective and can be occlusive systems with a lower profile and greater ease of use. Both techniques, angioplasty with stent (with filter or flow occlusion systems) and endarterectomy, are involved in cases of intracranial embolism per treatment.

New restriction foci (NF) in diffusion were present in half of the patients after CAS with cerebral protection and were most frequently located in the ipsilateral area (77.19%), suggesting that the filters did not prevent all microemboli. New restriction foci in DWI after CAS were located in regions (22.81%) different than in the angioplasty and were associated with diagnostic catheterization. Therefore, long neurointerventionist medical training should be required before CASs are performed.

The NF in DWI after CAS were mostly small in diameter (<10 mm in 91.53%) and were always clinically silent (100%) in our study.

The presence of cerebral infarcts in the T2 sequence in the initial MRI was the only factor that significantly predisposed the appearance of new restriction foci in DWI after CAS. Thus, the risk of microemboli was directly related to intrinsic factors of the patient. Other demographic factors and aspects related to the angioplasty technique were not statistically significant to the occurrence of NF in our study. There was a tendency for other factors, such as the triaxial access technique, asymptomatic patients, and an eccentric filter, to be involved in the appearance of a smaller number of NF after CAS.

The appearance of microemboli attributed to catheterization and not angioplasty with stent shows that proper training for medical specialists in cervical and cerebral circulation (neuro-interventionists) can be key to reducing risks for patients. General specialists in vessels (vascular surgeons) and coronary circulation (cardiologists) generally do not have specific training for cervicocerebral circulation; most of their training focuses on the aorta and coronary arteries, respectively. We therefore recommend that angiographies to diagnose cervical and cerebral circulation and carotid angioplasty be conducted by interventional neuroradiologists to reduce the risk of emboli.

To maintain cerebral flow during the endovascular carotid treatment, CAS with filter is the first choice in cases of serious stenosis. The use of occlusive systems is promising but requires more technical development to reduce the risks associated current systems.

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