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ORIGINAL ARTICLE **ÖZGÜN ARAŞTIRMA**

THE TOPOGRAPHY AND PREDICTORS OF POST-CONTRAST SULCAL FLAIR HYPERINTENSITIES IN THE SETTING OF CAROTID ARTERY STENTING

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ABSTRACT

INTRODUCTION: One major issue related to carotid artery revascularization procedures is their potential for inducing disturbances in blood brain barrier (BBB) permeability. The evaluation for sulcal contrast enhancement (SCE) on post-contrast fluid-attenuated inversion recovery (FLAIR) sequences is a commonly used approach to determine BBB integrity. In this study, we assessed the interplay between SCE, and clinical, perfusion and BBB permeability features in a series of patients undergoing carotid artery stenting, and also evaluated the topographic distribution of this phenomenon.
METHODS: Clinical information (including demographic data, cardiovascular risk factors, degree of stenosis, indication and timing of the procedure), together with pre- and immediate post- (<24 hours) procedural magnetic resonance imaging (MRI) data was prospectively collected in a consecutive series of patients. SCE was graded on post-contrast FLAIR sequences, and its relationship with hemodynamic (CBV, CBF, MTT) and parenchymal permeability (K-trans) changes was analyzed. Regions of contrast extravasation were semi-automatically outlined and co-registered to a standard template in order to determine the topography of SCE.
RESULTS: SCE on post-contrast FLAIR sequences was observed in 11 out of 42 patients (26%) prior to stenting, a feature that was independently related to a recent history (<30 days) of ischemic stroke (p=0.008) and lower degree of stenosis (p=0.014) in multivariate analyses. De novo or increased SCE following the procedure was seen in 22 patients (52%); increased permeability was primarily observed in the ipsilateral cortical watershed territories. No clinical or imaging features was predictive of SCE in the post-stenting period. The positive predictive value of de novo high-grade SCE for predicting post-procedural focal neurological symptoms was low [27% (95% CI, 17%-41%)].
DISCUSSION AND CONCLUSION: Our findings highlight that BBB dysfunction in the blood-CSF interface is a frequently common observation in the peri-stenting setting. Its relationship with perfusion, and BBB permeability alterations within the brain parenchyma itself, and its utility for predicting hyperperfusion syndrome is poor.
Keywords: Blood brain barrier permeability, carotid artery stenting, hyperperfusion syndrome, post-contrast FLAIR, sulcal contrast enhancement.

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KAROTİD ARTER STENTLEME SÜRECİNDE SAPTANAN POST-KONTRAST SULKAL FLAIR HİPERİNTENSİTELERİNİN TOPOGRAFİSİ VE BELİRLEYİCİLERİ

ÖZ

GİRİŞ ve AMAÇ: Karotid arter revaskülarizasyon prosedürleriyle ilgili önemli bir sorun, bu müdahalelerin kan beyin bariyeri (KBB) geçirgenliğinde bozulmalara neden olma potansiyelidir. Post-kontrast FLAIR sekanslarında sulkal kontrast parlamasının (SKP) değerlendirilmesi, KBB bütünlüğünü belirlemek için yaygın olarak kullanılan bir yaklaşımdır. Bu çalışmada, karotid arter stentlemesi yapılan bir dizi hastada SKP ile klinik, perfüzyon ve KBB geçirgenlik özellikleri arasındaki etkileşim ve sulkal kontrastlanmanın topografik dağılımı incelenmiştir.

YÖNTEM ve GEREÇLER: Ardışık bir hasta serisinde, hastaların klinik bilgileri (demografik veriler, kardiyovasküler risk faktörleri, stenoz derecesi, işlemin endikasyonu ve zamanlaması), işlem öncesi ve işlem sonrası (<24 saat) manyetik rezonans görüntüleme (MRI) verileri prospektif olarak toplanmıştır. Post-kontrast FLAIR sekanslarında değerlendirilen SKP derecesinin, hemodinamik (CBV, CBF, MTT) ve parankimal geçirgenlik (K-trans) değişiklikleriyle ilişkisi analiz edilmiştir. Kontrast ekstravazasyon bölgeleri yarı otomatik bir yöntem kullanılarak belirlenmiş ve standart bir şablona oturtularak topografi haritaları oluşturulmuştur.

BULGULAR: Kontrast sonrası FLAIR sekanslarında SKP, stent takılmadan önce 42 hastanın 11'inde (%26) gözlendi; bu özellik çok değişkenli analizlerde yakın zamanda geçirilmiş (<30 gün) iskemik inme öyküsü (p=0,008) ve daha düşük darlık derecesi (p=0,014) ile bağımsız olarak ilişkiliydi. Yirmi iki hastada (%52) işlem sonrasında yeni veya artmış SKP görüldü; artan geçirgenlik özellikle ipsilateral kortikal watershed bölgelerinde gözlendi. Stentleme sonrası dönemde gelişen SKP'yi hiçbir klinik veya görüntüleme özelliği öngöremedi. İşlem sonrası de novo yüksek dereceli SKP varlığının fokal nörolojik semptomları öngörme potansiyeli de düşük olarak saptandı [%27 (%95 GA, %17-%41)].

TARTIŞMA ve SONUÇ: Bulgularımız, kan-BOS arayüzündeki KBB disfonksiyonunun stent öncesi dönemde sıklıkla görülen bir bulgu olduğunu vurgulamaktadır. Bu bulgunun, perfüzyon ve beyin parankimindeki KBB geçirgenliği değişiklikleri ile ilişkisi ve hiperperfüzyon sendromunu öngörmedeki başarısı zayıftır.

Anahtar Sözcükler: Kan beyin bariyeri geçirgenliği, karotid arter stentleme, hiperperfüzyon sendromu, post-kontrast FLAIR, sulkal kontrastlanma.

INTRODUCTION

The treatment of carotid artery stenosis by endarterectomy or stenting is well known to induce a number of cerebral hemodynamic alterations in the distal vasculature. At the most extreme, increased cerebral blood flow accompanied by blood-brain barrier (BBB) dysfunction and fluid transudation into the interstitial space results in cerebral hyperperfusion syndrome (1,2). Therefore, monitoring of cerebral hemodynamics in the peri-revascularization setting has been the subject of multiple studies; however, these efforts were generally directed to evaluation of tissue perfusion dynamics (3-11), while less attention was paid to the alterations in BBB permeability within this context (12,13).

Blood-brain barrier permeability, which also is a key parameter in neuro-oncology or acute stroke imaging, can be assessed by various methodologies on magnetic resonance imaging (MRI). Perfusion-weighted imaging (PWI), in addition to providing information on cerebral hemodynamics, can also be used to evaluate tissue permeability by metrics like efflux rate of gadolinium (i.e. volume transfer constant, k-trans) (14). Alternatively, evaluation of contrast extravasation on T1-weighted, or preferably fluid-attenuated inversion recovery (FLAIR) sequences, provides a qualitative measure of BBB integrity (15). However, these two imaging modalities do not always correlate regarding the presence of BBB permeability (16). Furthermore, delayed contrast enhancement in cerebral sulci, which is relatively common after carotid stenting, is not directly predictive of cerebral hyperperfusion syndrome (13,17,18). In this study, we primarily assessed the interplay between sulcal contrast enhancement (SCE) on FLAIR images, and clinical, perfusion, and BBB permeability features in a series of patients undergoing carotid artery stenting, and also evaluated the topographic distribution of this phenomenon.

METHODS

This was a prospective study of patients undergoing carotid artery stenting for symptomatic or asymptomatic carotid artery disease. Brain MRI was performed with a 3.0 Tesla scanner (Ingenia, Philips Healthcare, Best, the

Netherlands) prior to and within 24 hours after the stenting procedure. The acquisition protocol for structural images included axial T2-weighted (W) turbo spin-echo (SE) (TR/TE:3000/100ms), axial T2-FLAIR (TR/TE/TI; 11000/125/2800ms), and axial diffusion-weighted imaging (DWI) (TR/TE: 2994/94ms, b=0 and 1500 s/mm2). In 33 patients, the structural imaging was followed by dynamic contrast-enhanced (DCE), and dynamic susceptibility contrast-enhanced (DSC) PWI studies. For DCE scan, 10 mL of gadolinium-based contrast media (gadoteric acid) was injected at a rate of 3 mL/s followed by 10 mL saline flush using an electronic power injector (OptiStar® Elite MR Contrast Delivery System, Mallinckrodt Pharmaceuticals, Hazelwood, MO) via 18-gauge antecubital venous access. DSC PWI, the details of which are previously reported as part of a separate study, was acquired 20 seconds after DCE imaging (19). T2-FLAIR was repeated 15 minutes after injection of contrast media, regardless of the acquisition of PWI studies. The study was approved by the local institutional review board. The data of the study will be made available upon reasonable request.

Clinical information, including demographic data, cardiovascular risk factors, degree of stenosis, prior history of stroke, and timing of the procedure, was collected for all patients. Post-contrast FLAIR images were evaluated for the presence or absence of sulcal hyperintensities. To quantify the extent of contrast enhancement in the subarachnoid space, we developed a scoring system based on the ASPECTS template (20); per this system sulci within each hemispheric cortical middle cerebral artery territory (M1 to M6), together with anterior and posterior cerebral artery territories were assigned score of 1 when there was evidence of contrast extravasation. Therefore, the score ranged from 0 to 16. In patients whom the interval between the two MRI studies was short, and there was still residual contrast enhancement in the sulci from the initial examination, the presence and degree of SCE in the post-stent MRI was evaluated in comparison to the pre-contrast FLAIR images of this second session. For the topographic distribution analyses, we coregistered post-contrast FLAIR images obtained at the post-stenting period to MNI152 T1-template [FSL-FLIRT; Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software (FSL, www.fmrib.ox.ac.uk/fsl) Linear Image Registration Tool] (21,22), and created masks of sulcal hyperintensities using semi-automated thresholding in each patient (MRIcro software; University of Nottingham, UK, www.mricro.com). The masks of all patients were then combined in a single template to display the probability maps. As an additional analysis, we evaluated the presence or absence of contrast enhancement within ocular structures, based on the recent interest in the field, and the interplay between BBB and blood-retina barrier dysfunctions (23,24).

Cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) maps were created from DSC PWI images, and measured within the middle cerebral artery masks, as described previously (19). The measurements were normalized with respect to the contralateral hemisphere. K-trans maps were obtained by semimanual postprocessing of DCE images on syngo.via VB30A (Siemens Healthcare, Berlin, Germany). Two regions of interest (ROI) with 20 mm in diameters were placed to lentiform nucleus and six cortical ASPECTS regions (M1 to M6) on the side of the revascularization procedure. K-trans values were determined from these ROIs, and the means were normalized to mirror ROIs in the contralateral hemisphere. Care was taken not to place ROIs on areas encompassing lesions.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Statistical Analysis: Categorical variables are expressed as n (%), and continuous variables are presented as median (interquartile range, IQR). Chi-square test and Mann-Whitney U test were used accordingly, to determine group-wise differences. Correlation analyses were performed by Spearman's test. Logistic regression analysis was used for multivariate analysis. A p value of <0.05 was considered statistically significant. Statistical analyses were performed by SPSS 16.0.

RESULTS

The study was conducted in 42 patients who underwent carotid artery stenting during the 24-month period from August 2014 to July 2016 in our center. The median (IQR) age of the study

population was 67 (61-72) years. Four patients had an occlusion of the contralateral internal carotid artery. Other baseline features of the study population are summarized in Table 1. Carotid stenting was performed for symptomatic stenosis in 31 (74%) patients; of these, the interval between the stroke and procedure was less than 30 days in 18 cases.

Table 1. Baseline clinical features of the study population.

	n=42
Female gender (n, %)	18 (43%)
Risk factors (n, %)	
Hypertension	33 (79%)
Diabetes Mellitus	20 (48%)
Hyperlipidemia	23 (55%)
Coronary Artery Disease	16 (38%)
Prior history of stroke (n, %)	31 (74%)
Degree of stenosis (median, IQR)	76 (69-81) %

Prior to stenting, SCE on post-contrast FLAIR images were visible in 11 (26%) patients. Enhancement was graded as 1 (per the ASPECTS cortical areas) in three patients, as 2 in one patient. and as ≥3 in seven patients. SCE was limited to the hemisphere distal to the stenotic carotid, except for two patients. The interplay between SCE, and baseline clinical and imaging features are summarized in Table 2.

Table 2. Clinical and imaging features of patients with or without sulcal contrast enhancement on FLAIR prior to stenting.

	Sulcal contrast enhancement		p
	Yes (n=11)	No (n=31)	
Age	69 (61-74) years	66 (61-72) years	0.516
Female gender	6 (55%)	12 (39%)	0.362
Hypertension	10 (91%)	23 (74%)	0.403
Diabetes mellitus	5 (46%)	15 (48%)	0.867
Hyperlipidemia	2 (18%)	21 (68%)	0.011
Coronary artery disease	6 (55%)	10 (32%)	0.191
Prior history of stroke	11 (100%)	20 (65%)	0.041
History of stroke ≤30 days	10 (91%)	8 (26%)	<0.001
Degree of stenosis	71 (63-74) %	79 (75-85) %	0.001
Plasma creatinine level mg/dl	0.7 (0.6-1.0)	0.9 (0.7-1.0)	0.252
CBV ratio*	1.03 (0.98-1.17)	1.06 (1.00-1.18)	0.468
CBF ratio*	0.78 (0.67-1.02)	0.68 (0.59-0.73)	0.013
MTT ratio*	1.21 (1.05-1.46)	1.48 (1.37-1.95)	0.007
K trans ratio*	0.98 (0.85-1.36)	1.12 (0.87-1.26)	0.620

*information available in 33 patients; the numbers signify the ratio with respect to the contralateral hemisphere.

The significant relationships detected on bivariate analyses between the presence of SCE, recent history of stroke, absence of hyperlipidemia, lower degree of stenosis, higher CBF and shorter MTT values stood out when the analyses were repeated taking into account the grade of contrast extravasation (Table 3). On multivariate analysis only a history of stroke within the last 30 days (OR 163, 95% CI 4-7104; p=0.008) and degree of stenosis (OR 0.84, 95% CI 0.73-0.97; p=0.014) were found to be significantly related to presence of SCE. We were not able to demonstrate any relationship of SCE with K-trans values.

Table 3. Relationship between SCE grade, and clinical and imaging features of patients prior to stenting.

	Grade of sulcal contrast enhancement
Age	p=0.304
Female gender	p=0.698
Hypertension	p=0.255
Diabetes mellitus	p=0.873
Hyperlipidemia	p=0.002
Coronary artery disease	p=0.101
Prior history of stroke	p=0.023
History of stroke ≤30 days	p=<0.001
Degree of stenosis	p=0.001 (r=-0.50)
Plasma creatinine level	p=0.551
CBV ratio*	p=0.464
CBF ratio*	p=0.004 (r=0.49)
MTT ratio*	p=0.002 (r=-0.54)
K trans ratio*	p=0.579

*Information available in 33 patients.

On MRI studies performed following carotid stenting, de-novo SCE on post-contrast FLAIR images was observed in 15 patients; in addition, 7 patients who already had enhancement prior to stenting showed a spatial increase in the extent of involvement. The grade of enhancement was evaluated as 1 in four patients, as 2 in two patients, as 3 in four patients, and as ≥4 in 12 patients. The topographic analysis of these newly developing enhancements after carotid stenting suggested the involvement of sulci neighboring the ipsilateral watershed territories (Figure 1). The comparison of these 22 patients (52%) with the remaining population in terms of clinical and imaging characteristics are summarized in Table 4, which highlights no significant association between any of the clinical or imaging parameters

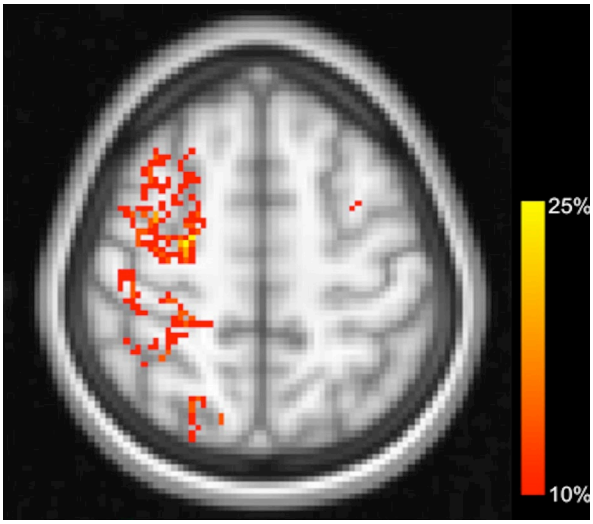

Figure 1. Voxel-wise probability distribution maps of voxels with sulcal contrast enhancement on FLAIR images. The radiological right side designates the hemisphere ipsilateral to the side of stenting.

and new onset or increased SCE. No change in our findings were observed when the analyses were repeated after grading the extent of enhancement (Table 5). A total of three patients (one with contralateral occlusion of the carotid artery) experienced focal neurological symptoms without any evidence of new ischemic lesions on the ensuing days, suggestive of hyperperfusion syndrome. There was no evidence of SCE prior stenting in any of these patients; however, all of them developed de novo enhancement on post-contrast FLAIR after carotid stenting. The grades of enhancement were 4, 7, and 8 in these patients. The positive predictive value of a de novo enhancement pattern ≥ grade 4 after stenting for focal neurological symptoms was 27% (95% CI, 17%-41%), while the negative predictive value was 100% (95% CI, 90%-100%).

Post-contrast FLAIR studies performed prior to stenting revealed enhancement in the anterior

Table 4. Clinical and imaging features of patients with or without sulcal contrast enhancement on FLAIR after stenting.

	De novo or increased sulcal contrast enhancement		p
	Yes (n=22)	No (n=20)	
Age	69 (62-75) years	66 (60-70) years	0.212
Female gender	7 (32%)	11 (55%)	0.129
Hypertension	17 (77%)	16 (80%)	1.000
Diabetes mellitus	10 (46%)	10 (50%)	0.768
Hyperlipidemia	10 (46%)	13 (65%)	0.204
Coronary artery disease	11 (50%)	5 (25%)	0.096
Prior history of stroke	17 (77%)	14 (70%)	0.592
History of stroke ≤30 days	11 (48%)	7 (35%)	0.327
Degree of stenosis	74 (66-80) %	79 (75-85) %	0.070
Plasma creatinine level	0.8 (0.7-1.0) mg/dl	0.7 (0.6-0.9) mg/dl	0.070
New post-procedural DWI lesions	7 (32%)	5 (25%)	0.625
Sulcal contrast enhancement on baseline MRI	7 (32%)	4 (20%)	0.384
CBV ratio on baseline MRI*	1.03 (0.99-1.13)	1.04 (0.99-1.24)	0.386
CBV ratio on post-stent MRI*	1.00 (0.96-1.10)	1.00 (0.95-1.09)	0.971
%change in CBV ratio*	-1 ([-7] – [2]) %	-5 ([-7] – [-2]) %	0.076
CBF ratio on baseline MRI*	0.74 (0.67-0.85)	0.68 (0.59-0.74)	0.129
CBF ratio on post-stent MRI*	0.93 (0.85-1.14)	0.94 (0.74-1.02)	0.588
%change in CBF ratio*	28 (5-43) %	36 (1-60) %	0.515
MTT ratio on baseline MRI*	1.39 (1.17-1.66)	1.46 (1.27-2.00)	0.210
MTT ratio on post-stent MRI*	1.07 (0.84-1.20)	1.12 (1.00-1.37)	0.342
%change in MTT ratio*	-21 ([-33] – [5]) %	-26 ([-41] – [-3]) %	0.447
K trans ratio on baseline MRI*	1.12 (0.91-1.27)	1.02 (0.82-1.21)	0.366
K trans ratio on post-stent MRI*	0.95 (0.73-1.07)	1.26 (0.83-1.65)	0.087
%change in K trans ratio*	-12 ([-42] – [10]) %	13 ([-22] – [65]) %	0.063

*Information available in 33 patients; the numbers signify the ratio with respect to the contralateral hemisphere.

chamber (aqueous humor) in 26 (62%) patients; seven of these were primarily unilateral and involved the side of stenosis in six cases; as a novel observation, there was enhancement in the wall of the posterior chamber of the globe in half of these cases (n=13) (Figure 2). We detected no enhancement in the vitreous humor in any of our patients. We were not able to identify any significant association between sulcal and ocular enhancement. Patients with enhancement in the wall of the posterior chamber were more likely to have history of diabetes (85% vs. 31%; p=0.002);

on the other hand, no such relationship was observed when the presence of any ocular enhancement was taken into account. No major change was observed regarding ocular contrast enhancement in the post-stenting period; there were only two additional patients who developed de novo ocular enhancement.

Table 5. Relationship between SCE grade, and clinical and imaging features of patients after stenting.

	Grade of sulcal contrast enhancement
Age	p=0.272
Female gender	p=0.299
Hypertension	p=0.361
Diabetes mellitus	p=0.494
Hyperlipidemia	p=0.376
Coronary artery disease	p=0.205
Prior history of stroke	p=0.492
History of stroke ≤30 days	p=0.490
Degree of stenosis	p=0.200
Plasma creatinine level	p=0.153
New post-procedural DWI lesions	p=0.695
Sulcal contrast enhancement on baseline MRI	p=0.835
CBV ratio on baseline MRI*	p=0.355
CBV ratio on post-stent MRI*	p=0.879
% change in CBV ratio*	p=0.133
CBF ratio on baseline MRI*	p=0.405
CBF ratio on post-stent MRI*	p=0.915
% change in CBF ratio*	p=0.681
MTT ratio on baseline MRI*	p=0.541
MTT ratio on post-stent MRI*	p=0.789
% change in MTT ratio*	p=0.669
K trans ratio on baseline MRI*	p=0.311
K trans ratio on post-stent MRI*	p=0.177
% change in K trans ratio*	p=0.102

*Information available in 33 patients.

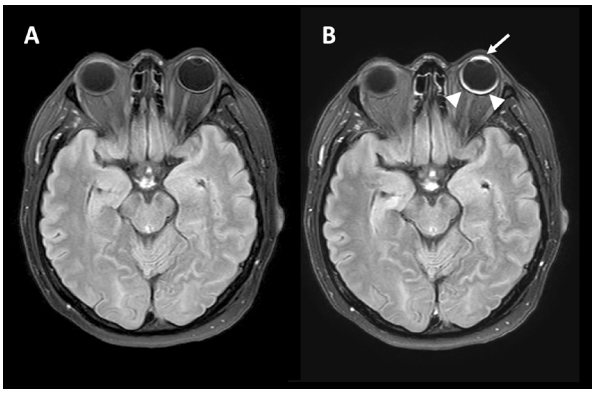

Figure 2. Enhancement is noted in the aqueous chamber (arrow) and posterior wall of the posterior chamber (arrowheads) of the left eye on post-contrast FLAIR images (B). No such hyperintensities are noted on pre-contrast FLAIR images (A).

DISCUSSION AND CONCLUSION

Alterations in BBB permeability are well-known during the periprocedural period in patients undergoing carotid revascularization. Herein, we studied the spatial and temporal aspects of this phenomenon using post-contrast FLAIR imaging and showed that BBB permeability issues already exist in the pre-stenting stage in patients who have suffered a recent stroke. On the other hand, in the post-stenting stage, no clinical or imaging feature that we analyzed was related to newly developing SCE on FLAIR images, which primarily involved the watershed territories.

Post-contrast FLAIR imaging, due to its higher sensitivity for detection of gadolinium in the cerebrospinal fluid (CSF) in comparison to post-contrast T1-W SE images, has now become one of the commonly used modalities to evaluate BBB dysfunction. Impairments in BBB permeability has been documented with this technique in various clinical settings, including acute ischemic stroke (15,25), transient ischemic attack (26), intracerebral hemorrhage (27), post-cardiac surgery (28), posterior reversible encephalopathy syndrome (29), meningeal diseases (30), and cognitive impairment (31). The utility of this imaging modality in patients undergoing carotid artery stenting was first evaluated by Wilkinson et al. (18) However, due to short-time interval between the pre- and post-procedural MRI studies, pre-contrast FLAIR images performed after stenting were contaminated by the delayed accumulation of gadolinium in CSF administrated during the pre-stenting scans, and the specific influence of stenting on BBB permeability could therefore not be analyzed in this initial report. Nonetheless, SCE on FLAIR images in patients undergoing carotid revascularization have been confirmed by later publications with an incidence ranging from 17% to 75% (13,32-35). Most of these patients remained neurologically asymptomatic, while widespread contrast enhancement was observed upon the retrospective review of the radiologic studies of patients with focal symptoms in these publications (17,32,33,36,37). Concordantly, in our study, where we used a grading algorithm to quantify the magnitude of SCE, focal neurological symptoms consistent with hyperperfusion syndrome were evident only in those patients with involvement of

ASPECTS ≥4 territories. It should be noted that this observation can only be considered preliminary and is not a specific finding to predict development of hyperperfusion syndrome.

Although SCE on FLAIR images is considered to reflect increased BBB permeability, the presence of this imaging feature does not only poorly correlate with the clinical end point (i.e. focal neurological symptoms or hyperperfusion syndrome), but also with the perfusion and permeability metrics on imaging, as evaluated in our study. Studies performed in acute stroke patients have highlighted that the presence of enhancement on post-contrast FLAIR studies (known as hyperintense acute reperfusion marker, or HARM) despite its close association with reperfusion, is not always predictive of hemorrhagic transformation (15,25,38,39). In contrast, presence of an evidence for BBB dysfunction within the brain parenchyma itself, rather than the sulci, is more predictive of hemorrhagic complications (38). Other studies were also not successful in showing a close relationship regarding the presence of SCE, and changes in permeability or perfusion of the brain parenchyma (16,17,33,36). All of these findings, together with the evidence from experimental studies (40), suggest that the underlying pathophysiology and resulting clinical implications might be different for BBB permeability issues occurring in the parenchyma or CSF interface. While the former is considered as a harbinger of devastating complications, the latter might signify a temporary and more benign dysfunction that is primarily localized to the watershed areas.

In order to tease out the specific contribution of carotid artery stenting to BBB permeability changes, the baseline situation prior to the procedure should be evaluated as well. Similar to our observations, SCE is commonly observed in recently symptomatic carotid stenosis patients (13,18). This is not unexpected due to close correlation between BBB dysfunction and acute stroke. However, SCE is not an unequivocal characteristic of all recently symptomatic carotid stenosis patients, suggesting the role of other factors in this interplay. One possible candidate in this regard is the degree of carotid stenosis, as demonstrated by our analyses. Data accumulating over the years have highlighted differences with respect to plaque characteristics, stroke mechanisms, and infarct patterns among patients with lower- and higher degrees of carotid stenosis (41,42). The more common observation of BBB dysfunction in embolic stroke etiologies (43), and the unstable nature in moderately stenotic yet symptomatic plaques, might underlie our observation of an inverse relationship between the degree of stenosis and prevalence of SCE at baseline. As an additional note, the presence of SCE at the pre-procedural setting was not related to any post-procedural complications like focal neurological symptoms in our cohort.

Contrast enhancement in ocular structures in the setting of central nervous system diseases, possibly reflecting the common ground of pathologies affecting blood retina barrier and BBB, has been a recent research interest in the literature (23,24,44). Gadolinium leakage into ocular structures (GLOS), involving the aqueous or vitreous chambers, has been reported in patients suffering from BBB permeability issues such as acute stroke (23), or chronic lacunar stroke (24). Although it was not the primary focus of our study, we evaluated our cohort from this perspective as well. We found that the carotid stenting procedure itself rarely triggered GLOS, at least in the immediate post-procedural period. On the other hand, similar to a prior report in the literature (45), GLOS was not uncommonly observed in carotid stenosis patients prior to stenting; notably it was a stable radiological finding that was consistently observed both in the pre- and post-procedural MRI's and generally involved both globes. When there was asymmetric involvement, it was generally on the side of stenosis. As a novel finding, we identified enhancement in the wall of the posterior chamber, primarily in patients with a history of diabetes mellitus. This pattern has not been reported in the prior literature focusing on GLOS; however, in those studies GLOS was generally evaluated hours after contrast administration (23,24,45), in contrast to our study where post-contrast images were obtained after 15 minutes. In a subset of patients who had follow-up images at later time points, we observed contrast leakage into the vitreous chamber in all cases with posterior wall enhancement (results not reported). Therefore, we believe that this radiologic phenomenon might reflect the presence of an extremely permeable blood retina barrier, that might even be detected from the very early time points after contrast administration. Previous studies have indeed suggested a temporal

evolution of GLOS, where contrast enhancement starts from the aqueous chamber and then progresses into the vitreous chamber as time passes by (23). Enhancement in the wall of the posterior chamber might be one of the initial events in this sequential process, especially in certain patients like diabetics, where retina blood barrier problems are encountered frequently. Finally, we were not able to detect any association between GLOS and SCE, contrary to the previous literature (23,24,45); this discrepancy might be the result of the different timing algorithms used in our study, as mentioned above.

In conclusion, our findings suggest that SCE on FLAIR images, suggestive of increased BBB permeability in the blood-CSF interface is a common radiological phenomenon in the peri-stenting setting. Its correlation with perfusion and BBB permeability alterations within the brain parenchyma itself is poor, and unless extensive is rarely accompanied by focal neurological findings. Despite being reported in a multitude of neurological disorders, we have still not entirely understood the pathophysiological aspects and clinical implications of gadolinium leakage into the subarachnoid space. Future studies with larger numbers of patients are needed to tease out the role of candidate mechanisms like inflammation, hemodynamic alterations, or neuronal and endothelial injury that might explain this radiological observation signifying a dysfunctional blood-brain barrier.

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Ethics

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