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ORIGINAL PAPER

Associations between carotid intraplaque hemorrhage and new ipsilateral ischemic lesions after carotid artery stenting: a quantitative study with conventional multi-contrast MRI

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Abstract

The risk of cerebral embolism after CAS in patients with carotid IPH is still controversial. This study was to further investigate the relationship between IPH and new ipsilateral ischemic lesion (NIIL) after CAS, and to perform a volumetric analysis of IPH for predicting the risk of NIIL following CAS. One hundred and seventeen patients with carotid stenosis undergoing CAS were prospectively enrolled. Preprocedural multi-contrast carotid MRI was performed. NIIL was evaluated by brain DWI before and after CAS. IPH volume, wall volume at the plaque (WV_{plaque}) and relative IPH volume were calculated. Associations between IPH and postprocedural NIIL were studied. NIILs were shown in 52 patients. IPH were identified in 53 patients. NIILs were found more frequently in IPH-positive (33/53, 62.3%) than in IPH-negative patients (19/64, 29.7%, $p<0.001$). There was no significant difference of WV_{plaque} between NIIL-positive and NIIL-negative patients (1166.6 ± 432.0 mm^3 vs 1124.6 ± 410.4 mm^3, $p=0.592$). The IPH volume from NIIL-positive group was significantly larger than that of NIIL-negative group (252.8 ± 264.9 mm^3 vs 59.3 ± 131.1 mm^3, $p<0.001$), with also higher relative IPH volume (20.4 ± 19.1% vs 5.7 ± 12.2%, $p<0.001$). ROC curve showed that 183.45 mm^3 of the IPH volume was the most reliable cutoff value for predicting NIIL with a specificity of 92.3% and a positive predictive value of 86.1%. Larger IPH volume is associated with increased risk of NIIL after CAS procedure. Quantification of IPH volume may be useful for predicting cerebral ischemic events after CAS.

Keywords New ipsilateral ischemic lesions · Carotid artery stenting · Intraplaque hemorrhage volume · Carotid plaque

Abbreviations

CAS	Carotid artery stenting
CEA	Carotid endarterectomy
CI	Confidence interval
IPH	Intraplaque hemorrhage
NIIL	New ipsilateral ischemic lesion
ROC	Receiver operating characteristic
TOF	Time-of-flight
WV	Wall volume

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Introduction

Carotid atherosclerosis is a major cause of ischemic stroke. Carotid endarterectomy (CEA) has been the primary method for treating severe carotid artery stenosis and preventing stroke, but recently, carotid artery stenting (CAS) is increasingly being used an alternative to CEA with the advantages of less invasiveness, reduced risk for postoperative wound complications, and a shorter duration of hospital stay [1]. Although earlier clinical trials [2, 3] have shown noninferiority of CAS as opposed to CEA in the prevention of stroke, higher incidence of new ipsilateral ischemic lesion (NIIL) in the brain during CAS has been reported using diffusion-weighted imaging (DWI) [4]. It may represent greater amount of ischemic burden and reflects a higher rate of cerebral events [5].The clinical significance and implication of NIIL after CAS used to be unclear, but recent studies have suggested that NIIL can increase the risk of dementia, cognitive impairment, future or recurrent cerebrovascular events, and mortality [6–8]. Therefore, in patients with carotid atherosclerosis planning for revascularization, choosing the optimal treatment is critical in considering the benefits and risks of each intervention.

Vulnerable plaque components may influence the risk of developing NIIL after revascularization [9]. Previous studies have demonstrated that hyperintense components on time-of-flight (TOF) or T1-weighted black-blood MR imaging, representing intraplaque hemorrhage (IPH), were associated with an increased risk of subsequent NIIL following CAS [10–12]. Yet other studies [13, 14] found that IPH identified by TOF or MPRAGE was not a significant risk factor for cerebral embolism, and placement of CAS was safe in these patients with high-grade carotid stenosis and IPH. In order to further elucidate the relationship between IPH and NIIL after CAS, we conducted this prospective study in 117 patients with conventional high-resolution multi-contrast MRI to determine whether IPH is associated with NIIL. If they were related with each other, the next step was to test our hypothesis that the volume of IPH in the plaque may be another important indicator for distal embolism after CAS.

Materials and methods

Study population

This prospective study included 122 consecutive patients with carotid stenosis between January 2015 and December 2017. All the patients had asymptomatic carotid stenosis of > 70% or symptomatic carotid stenosis of > 50% assessed with angiography (NASCET criteria [15]). A patient with carotid artery stenosis is considered symptomatic if the patient has transient or permanent focal neurologic symptoms related to the ipsilateral retina or the cerebral hemisphere [16]. This study was approved by the institutional ethics committee and informed consent was obtained from all patients prior to recruitment. All patients underwent carotid plaque MRI within 7 days before CAS. During this period, there were no new ischemic events such as transient ischemic attacks or strokes. DWI of the brain was performed at the same day of plaque MRI and repeated within 72 h after CAS.

Carotid plaque MRI protocol

Carotid plaque MRI was performed on a 3-Tesla MR scanner (Magnetom Verio; Siemens, Erlangen, Germany) with an 8-channel carotid surface coil (Shanghai Chenguang Medical Technologies, Shanghai, China). All patients underwent carotid plaque multi-contrast MRI (T1WI, T2WI and TOF) centered at the carotid bifurcation to obtain cross-sectional images of the carotid arteries. All sequences were performed with FOV of 160 × 160 mm, slice thickness of 2 mm, matrix of 256 × 256, in-plane resolution of 0.63 × 0.63 mm^2, and longitudinal coverage of 36 mm (18 slices). Parameters for different imaging sequences were as follows: (1) T1W turbo spin-echo (TSE): TR/TE 800/12 ms, acquisition time 3 min 20 s; (2) T2W TSE: TR/TE 4000/59 ms, echo spacing 15.1 ms, echo train length 18, bandwidth 133 Hz/pixel, flip angle 180°, acquisition time 3 min 40 s; (3) TOF: TR/TE 26/3.23 ms, flip angle 25°, acquisition time 2 min 33 s. The total scan time for carotid plaque MRI was 9 min 33 s.

DWI of the brain was acquired with a 16-channel head coil and an echo-planar sequence with the following parameters: TR/TE 6400/86.0 ms, slice thickness 5 mm, slice spacing 1.5 mm, b value 0 and 1000 s/mm^2, FOV 220 × 220 mm, bandwidth 1172 Hz/pixel and scanning time 46 s.

CAS procedure

All CAS procedures were performed by one experienced vascular surgeon. They were carried out with the patient under local anesthesia via the percutaneous transfemoral route. Aspirin (100 mg/d) and clopidogrel (75 mg/d) were given to the patients for a minimum of 3 days before the procedure. Systemic anticoagulation was initiated with a 3000-U bolus of intravenous heparin followed by a 1000-U/h infusion. Cerebral angiography was performed before stent placement to evaluate cerebral blood flow. A 6-8F guiding catheter was placed in the ipsilateral common carotid artery proximal to the carotid stenosis. Angiography was performed to evaluate the severity of carotid stenosis and

to observe the surface morphology of the plaque. Two different types of distal embolic protection devices were used: Emboshield (Abbott Vascular, Abboott Park, Illinois) and Filterwire EZ (Boston scientific, Natick, MA). Pre-dilation of the internal carotid lesion was done with a 4–6 mm balloon catheter. Three types of stents were deployed in the stenotic lumen: RX Acculink (Abbott Vascular, Abboott Park, Illinois), Wallstent (Boston Scientific, Natick, MA) and Precise (Johnson & Johnson, Cordis, Minneapolis, MN). Angiography immediately after CAS showed a residual diameter stenosis of < 30% in all patients.

MRI image evaluation

Two radiologists (Y.D. and X.B.) with 7 and 5 years of experience in plaque imaging, who were blinded to patients' clinical information and treatment option, reviewed all carotid plaque MR images. Image quality was independently rated on a 4-point scale (1 = non-diagnostic, 2 = poor, 3 = good, 4 = excellent) determined by the delineation of arterial wall, luminal margin and plaque components, as well as the presence of motion, flow, and pulsation artifacts. Images with a rating < 2 were excluded from the study.

Multi-contrast images of the carotid plaque were transferred to a personal computer equipped with a commercially available software (MRI-Plaque View, VPDiagnostic Inc., Seattle, WA, USA) for plaque analysis. These two radiologists matched and registered the carotid plaque images by using the carotid bifurcation as a landmark. The inner and outer wall boundaries of the carotid arteries at the plaque were outlined automatically by the software, and modified if necessary by the reviewers after reaching a consensus.

After that, regions of IPH were determined and delineated by a radiologist (P.L.) with 8 years of experience after reviewing all multi-contrast images. Compared with the adjacent sternocleidomastoid muscle, fresh or recent IPH appears hyperintense on both TOF and T1WI and varies from hypointense to hyperintense on T2WI according to the standard criteria [17, 18]. We used a cutoff value of signal intensity 50% greater than sternocleidomastoid muscle to define high-intensity signal in plaque. Whereas other intraplaque components, including lipid-rich necrotic core, calcification and fibrosis, usually appear either hypo- or isointense on TOF and T1WI [19]. Since T1WI shows the carotid lumen and plaque morphology more clearly, IPH areas were delineated manually on T1WI.

The wall volume at the carotid plaque (WV_{plaque}) and the volume of IPH were calculated by the software by summing the products of cross-sectional areas and slice thicknesses. The relative IPH volume (IPH volume/WV_{plaque} × 100%) was obtained subsequently. Based on the presence of IPH, these patients were divided into IPH-positive and IPH-negative groups. Ulcers on the plaque surface were also recorded.

Three months after the initial review, MR images of 15 randomly selected subjects from IPH-positive group were reevaluated separately by the same radiologist (P.L.) with 8 years of experience and another radiologist (A.J.) with 3 years of experience. IPH volume was measured again to assess inter- and intra-observer agreement.

The NIIL was defined as the newly appeared hyperintense signal in the brain after comparing pre- and post-CAS DWIs by the two same radiologists (P.L. and A.J.) with 8 and 3 years of experience through consensus interpretation.

Statistical analysis

Continuous variables were presented as means ± standard deviations. Categorical data were summarized as counts and percentages and compared using the Chi square test. Comparisons of continuous variables between cohorts were performed using an unpaired Student *t* test. Receiver operating characteristic (ROC) curves were used to determine the cutoff value of IPH volume and relative IPH volume in prediction of NIIL after CAS. Statistical significance was defined as $P < 0.05$. Interobserver agreement in the evaluation of image quality was assessed by using the Cohen K test. To determine inter- and intra-observer reproducibility in IPH volume measurements, the intraclass correlation coefficient was calculated to determine the agreement between 2 measurements. All statistical analyses were performed using SPSS 21.0 (IBM, Chicago, IL).

Results

The scoring of image quality for multi-contrast plaque imaging was 3.21 ± 0.89. In 117 out of 122 patients (95.9%), image quality was rated excellent or good, while 5 cases were excluded from further study due to poor image quality caused by artifacts or a limited signal-to-noise ratio on T2WI or TOF. There was excellent inter-observer agreement in the rating of image quality (ICC = 0.90). These 117 patients (104 males and 13 females, 52 to 88 years old) were subject to further analysis.

Patient demographics with and without IPH were summarized in Table 1. There was no significant difference in age, gender, major cardiovascular risk factors and smoking between the two groups. The other baseline characteristics including stenosis degree, plaque ulcer, aortic arch morphology, stent and protection device were also similar. The patient characteristics of the NIIL-positive and NIIL-negative groups were shown in Table 2 and there was no significant difference between the two groups in all the demographics and clinical factors.

Technical success of CAS was achieved in all these 117 patients. NIIL was detected on DWI in 52 of 117 (44.4%)

Table 1 Patient demographics and clinical information of IPH-positive and IPH-negative groups

	IPH (+) (n = 53)	IPH (−) (n = 64)	*P* value
Age, years	69.8 ± 7.1	68.1 ± 7.8	0.215
Gender			
Male, n (%)	50 (94.3)	54 (84.4)	0.880
Medical history			
Hypertension, n (%)	45 (84.9)	50 (78.1)	0.350
Dyslipidemia, n (%)	6 (11.3)	5 (7.8)	0.742
Diabetes mellitus, n (%)	25 (47.2)	24 (37.5)	0.291
Previous or present smoker, n (%)	20 (37.7)	19 (29.7)	0.358
Ischemic heart disease, n (%)	15 (28.3)	5 (7.8)	0.222
Symptomatic events, n (%)	29 (54.7)	40 (62.5)	0.394
Ulcer, n (%)	6 (11.3)	12 (18.7)	0.268
Stenosis, %	80.2 ± 11.8	77.0 ± 13.5	0.186
50–70, n (%)	17 (32.1)	19 (29.7)	
70–90, n (%)	14 (26.4)	23 (35.9)	
90–100, n (%)	22 (41.5)	22 (34.4)	
Aortic arch type			0.605
I, n (%)	25 (47.2)	33 (51.6)	
II, n (%)	19 (35.8)	21 (32.8)	
III, n (%)	9 (17.0)	10 (15.6)	
Embolic protection devices			0.390
Emboshield, n (%)	41 (77.4)	45 (70.3)	
Filterwire EZ, n (%)	12 (22.6)	19 (29.7)	
Stent			0.330
Rx Acculink, n (%)	21 (39.6)	20 (31.3)	
Wallstent, n (%)	15 (28.3)	19 (29.7)	
Precise, n (%)	17 (32.1)	25 (39.1)	

Note Values are number of patients (%) or mean ± standard deviations
*IP*H intraplaque hemorrhage

Table 2 Patient demographics and clinical information of NIIL-positive and NIIL-negative groups

	NIIL (+) (n = 52)	NIIL (−) (n = 65)	*P* value
Age, years	69.4 ± 6.3	68.4 ± 8.4	0.458
Gender			
Male, n (%)	45 (86.5)	59 (90.8)	0.469
Medical history			
Hypertension, n (%)	43 (82.7)	52 (80.0)	0.711
Dyslipidemia, n (%)	4 (8.0)	7 (10.8)	0.571
Diabetes mellitus, n (%)	22 (42.3)	27 (41.5)	0.933
Previous or present smoker, n (%)	19 (36.5)	20 (30.8)	0.985
Ischemic heart disease, n (%)	11 (21.2)	9 (13.8)	0.525
Symptomatic events, n (%)	28 (53.8)	41 (63.1)	0.313
Ulcer, n (%)	5 (10.0)	13 (20.0)	0.122
Stenosis, %	78.9 ± 12.3	78.1 ± 13.3	0.708
50–70, n (%)	14 (26.9)	22 (33.8)	
70–90, n (%)	19 (36.5)	18 (27.7)	
90–100, n (%)	19 (36.5)	25 (38.5)	
Aortic arch type			0.975
I, n (%)	26 (50.0)	32 (49.2)	
II, n (%)	18 (34.6)	22 (33.8)	
III, n (%)	8 (15.4)	11 (21.2)	
Embolic protection devices			0.075
Emboshield, n (%)	34 (65.4)	52 (80.0)	
Filterwire EZ, n (%)	18 (34.6)	13 (20.0)	
Stent			0.243
Rx Acculink, n (%)	16 (30.8)	25 (38.5)	
Wallstent, n (%)	13 (25.0)	21 (32.3)	
Precise, n (%)	23 (44.2)	19 (29.2)	

Note Values are number of patients (%) or mean ± standard deviations
NIIL new ipsilateral ischemic lesion

patients; 46 patients had ipsilateral lesions and 6 patients had bilateral lesions. The average total number of clinically silent NIIL per patient was 2. IPH was detected in 53 out of 117 patients (45.3%). NIILs were found significantly more frequently in IPH-positive patients (33/53, 62.3%) (Fig. 1) than in IPH-negative patients (19/64, 29.7%, $p < 0.001$). The pre-procedural symptomatic group showed a similar incidence of NIIL after CAS with the asymptomatic group (33/69, 47.8% vs 19/48, 39.6%, P = 0.38).

The mean WV_{plaque} in NIIL-positive and NIIL-negative groups was 1166.6 ± 432.0 mm^3 and 1124.6 ± 410.4 mm^3 respectively with no significant difference between them ($p = 0.59$). The IPH volume in NIIL-positive group was significantly larger than that in NIIL-negative group (252.8 ± 264.9 mm^3 vs 59.3 ± 131.1 mm^3, $p < 0.001$). Receiver operating characteristic (ROC) curve analysis indicated that a diagnostic sensitivity of 59.6%, a specificity of 92.3%, a positive predictive value (PPV) of 86.1%, a negative predictive value (NPV) of 74.1%, and an area under the curve (AUC) of 0.73 (95% CI: 0.63–0.82) was achieved, when the cutoff value of IPH volume was 183.45 mm^3 (Fig. 2a).

The relative IPH volume for NIIL-positive group was also significantly higher than that for NIIL-negative group (20.4 ± 19.1% vs 5.7 ± 12.2%, $p < 0.001$). ROC curve analysis showed that when the cutoff value of the relative IPH volume for predicting NIIL was 19.9%, the sensitivity, specificity, PPV and NPV were 55.8%, 90.8%, 72%, and 82.9%, respectively. An AUC of 0.72 (95% CI: 0.62–0.81) was obtained (Fig. 2b).

Both intra- and inter-observer agreements for measurement of IPH volume (ICC, 95% CI) were high (0.92, 0.76 to 0.97; 0.85, 0.61 to 0.95).

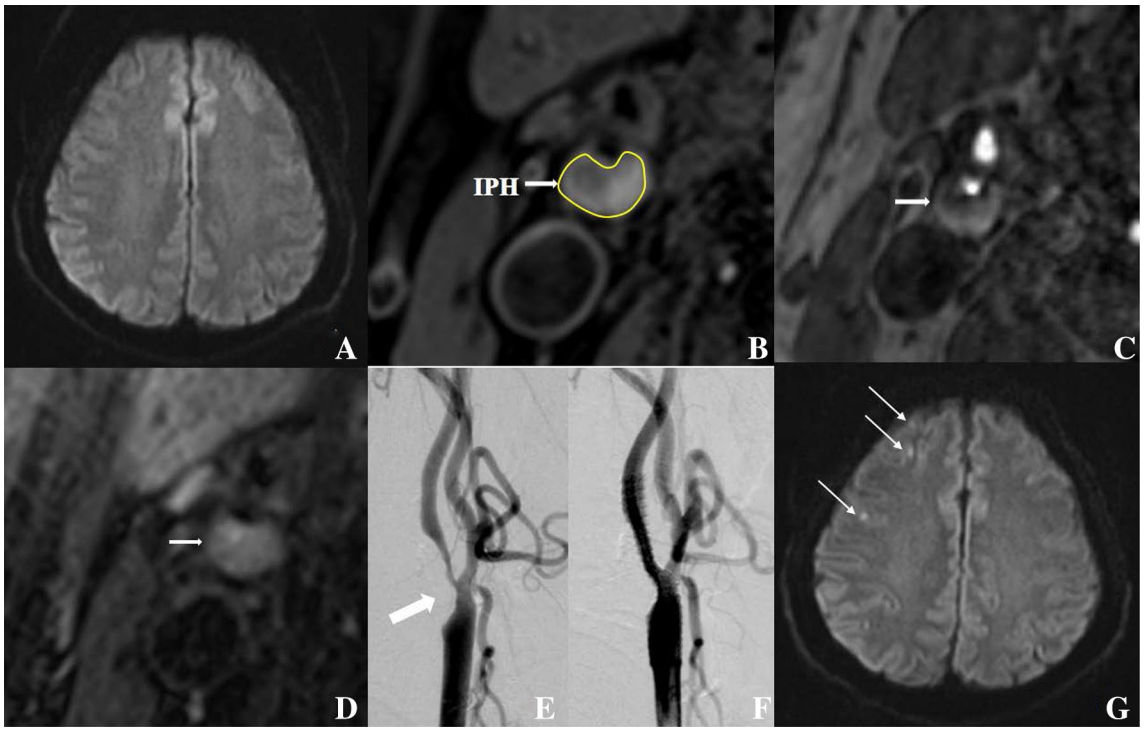

Fig. 1 A 61-year-old man with acute new ischemic lesions after carotid artery stenting. Diffusion-weighted image of the brain before carotid artery stenting (**a**) shows normal findings. T1-weighted (**b**), T2-weighted (**c**) and time-of-flight (**d**) multi-contrast images show the hyper-intense intraplaque hemorrhage (white arrows). The area of intraplaque hemorrhage is delineated on T1-weighted image (yellow contour). Pre-(**e**) and post-stenting (**f**) angiograms show the severe stenosis of the right carotid artery (white arrow) and restoration of the vessel lumen after placement of the stent. Diffusion-weighted image of the brain after the procedure (**g**) shows new ipsilateral ischemic lesions in the right frontal and parietal lobes (white arrows)

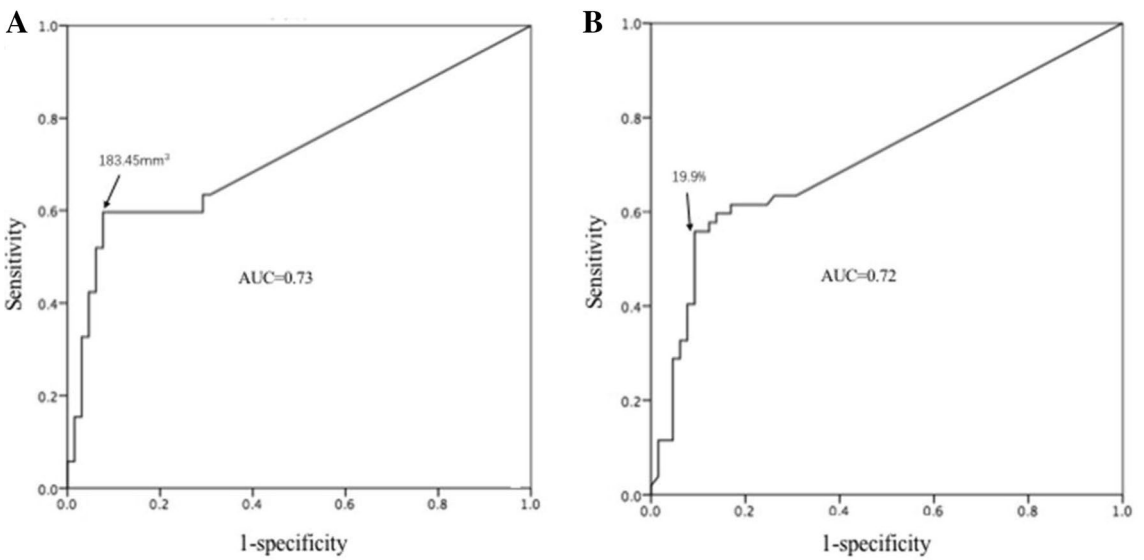

Fig. 2 ROC curve analysis of IPH volume (**a**) and relative IPH volume (**b**) for prediction of new ipsilateral ischemic lesion after carotid artery stenting. The area under the curve (AUC) of IPH volume is 0.73. ROC curve analysis indicates that an IPH volume of 183.45 mm^3 is the most reliable cutoff value for predicting ischemia after the stenting. Meanwhile for relative IPH volume, the AUC is 0.72 and the most reliable cutoff value is 19.9%

Discussion

This study demonstrated that IPH shown by multi-contrast MRI was associated with NIIL following protected CAS. By using quantitative plaque analysis, this study further demonstrated that both IPH volume and relative IPH volume were significantly larger in NIIL-positive than in NIIL-negative group. Cutoff values of IPH volume and relative IPH volume for predicting NIIL were also obtained. Quantitative MRI evaluation of carotid plaque hemorrhage may help exclude patients at high risk for stroke after CAS. To the best of our knowledge, this is the first report to examine the relationship between volume of IPH and the risk of post-CAS stroke, and to use IPH quantification for the risk prediction.

Being less invasive, CAS has emerged as a valid alternative to CEA in high surgical risk patients. However, the major concern of CAS is its high incidence of distal embolism even with currently wider use of stroke prevention therapies, improved patient selection and growing operator expertise [20]. In the present study, as high as 44.4% of the patients developed NIILs after CAS with embolic protection device. This high incidence of emboli shed to the brain was thought to be related to the shear force on the plaque during stent deployment [21]. Therefore, special attention should be paid to the vulnerable plaque, since it is associated with an increased risk of cerebral thromboembolism even without intervention [11]. Vulnerable plaque is characterized by the presence of a lipid-rich necrotic core (LRNC), ruptured fibrous cap, and IPH in particular [22]. IPH is caused by the disruption of the newly formed microvessels in the plaque. It promotes destabilization and growth of the plaque and increases the risk for cerebrovascular events [23–25]. However, studies showed conflicting results regarding the relationship between IPH and the risk of NIIL after CAS.

One recent study [13] found that IPH identified by MPRAGE was not a significant risk factor for NIIL since there was no significant difference in the incidence of NIIL after CAS between IPH-positive and IPH-negative groups. Similar results have been reported in an earlier study based on TOF-MRA [14], which indicated the safety of protected CAS in patients with carotid IPH. However, they did not quantify the amount of IPH which could influence the risk of NIIL. On the contrary, other studies demonstrated the association between IPH and NIIL. Yoshimura et al. [12, 26] reported a high intensity signal on TOF-MRA was associated with new ischemic events after CAS. Another study [10] showed that high signal intensity in the plaque on T1W black-blood MRI, which was attributed to both IPH and LRNC, was a useful predictor of NIIL after CAS. They further calculated the ratio of the signal intensity of the carotid plaque to that of sternocleidomastoid muscle, and found that a value of 1.25 was the most reliable cutoff value for predicting the NIIL after CAS. In these previous studies, carotid IPH was determined with only one MR imaging sequence, either TOF-MRA or T1WI, rather than a multi-contrast protocol. However, our present study employed the standardized multi-contrast MRI and defined IPH as hyperintensity on both T1WI and TOF which could exclude the interference from the signals of LRNC after incorporating the findings on T2WI as well. Furthermore, since T1WI shows the borders of IPH more clearly than TOF images, we measured the volume of IPH on T1WI.

All CAS procedures in the current study were performed by the same experienced vascular surgeon with more than 10 years of experience. Patients' baseline characteristics including cardiovascular risk factors, carotid stenosis and plaque ulcer between IPH-positive and IPH-negative groups were not significantly different. Like a previous study [12], NIILs on DWI were not significantly associated with preprocedural symptomatic lesions. After exclusion of these confounding factors which may lead to bias, we believe the validation of the association between IPH and NIIL should be convincing. With a specialized plaque analysis software, we measured the volumes of IPH. From the analysis of ROC curves, an IPH volume of 183.45 mm^3 was considered as the optimal cutoff value for predicting the NIIL after CAS with a high specificity and positive predictive value. The relatively poor sensitivity may be explained by the fact that other vulnerable components such as thin fibrous cap, large necrotic core and inflammation could also play an important role in the development of distal embolism after CAS. Although these components were not taken into consideration in this study, we demonstrated that patients with larger volume of IPH carried an increased risk of NIIL. A study by Yoshimura et al. [26] suggested that CEA should be selected for IPH positive plaques, whereas CAS for plaques without IPH to reduce post-CAS ischemic events. Our study further indicated that CAS could be risky for carotid plaques with large IPH volume exceeding the cutoff value, whereas it might be safe in low-risk plaques with small amount of IPH. Future prospective studies should be performed to confirm the usefulness of this IPH volume for selection of appropriate therapeutic modalities.

There were several limitations of this study. First, our study was limited by small sample size. Long-term follow-up of these patients was not available since the focus of this study was on the ischemic complications immediately after CAS. Second, IPH was identified without histologic reference, because it was not possible in patients with CAS. But T1WI and TOF are well-established and widely accepted MR sequences for detection of IPH, which have been validated by histology [17, 27, 28]. Third, only IPH was considered as a vulnerable feature in this study, other

risk components including ruptured fibrous cap, LRNC and inflammation may also be associated with subsequent cerebrovascular events. A multivariate logistic regression analysis with contrasted-enhanced MRI is warranted to investigate their associations in the future. But the quantification of these components is technically more challenging and contrasted-enhanced MRI should be used. Fourth, MPRAGE which is more sensitive to hemorrhage, was not added in this standardized multi-contrast protocol since it was not available at the beginning of this study. Fifth, based on different clinical settings, several kinds of stents and protection devices were used which may cause some bias, in spite of no significant difference between the two groups regarding the use of these facilities.

Conclusions

Our study confirms that carotid IPH is associated with the incidence of NIIL following CAS. Quantification of IPH volume may be useful for predicting the risk of NIIL after CAS. This study suggested that IPH should be evaluated and quantified with MRI before CAS procedures.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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