

Associations between intraplaque hemorrhage and other high-risk plaque features in atherosclerotic plaques

The Neuroradiology Journal
2025, Vol. 0(0) 1–6
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DOI: 10.1177/19714009251338634
journals.sagepub.com/home/neu



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Abstract

Background: Little is known about the association between intraplaque hemorrhage (IPH) and other features of high-risk carotid atherosclerotic plaques, such as the presence of plaque ulceration, plaque enhancement, and lipid-rich necrotic core (LRNC). This study set out to assess the relationship between IPH and other vulnerable plaque features.

Materials and Methods: A retrospective review was done of 102 patients with IPH in one or both of the internal carotid arteries (ICA) on neck MRA between 1/1/2016 and 3/31/2021. IPH was defined as a $\geq 200\%$ signal intensity of the adjacent sternocleidomastoid muscle on MPRAGE images. All ICA plaques were assessed for the presence or absence of IPH, plaque ulceration, plaque enhancement, and LRNC, as well as IPH volume. IPH volume was measured manually by outlining the region of interest.

Results: A total of 102 patients were included, with 88 (86.3%) being male. The average age was 73.5 years (SD = 9.0). Both IPH and LRNC were more commonly seen in the left carotid artery ($p = .018$ and $p = .047$, respectively). For right-sided ICAs, there was a significant association between IPH and LRNC ($p < .0001$). Lesions without IPH were more likely to have plaque enhancement than lesions with IPH ($p = .04$). For left-sided ICAs, there was also a significant association between the presence of IPH and LRNC ($p < .0001$).

Conclusions: There is a significant association between the presence of IPH and LRNC. An inverse relationship was found between the presence of IPH and plaque enhancement for right-sided plaques. No associations were found between IPH and plaque ulceration.

Keywords

Intraplaque hemorrhage, high-risk atherosclerotic plaques, carotid artery disease

Introduction

Carotid artery atherosclerosis is a common cause of ischemic stroke and transient ischemic attack.¹ Although research has historically focused on the degree of luminal narrowing in ischemic cardiovascular disease, it is now well-established that certain plaque characteristics make these more or less vulnerable to rapid changes and ipsilateral neurologic symptoms.² Many of these so-called “high-risk” plaque features have been identified, including lipid-rich necrotic cores (LRNCs), ulcerated fibrous caps, plaque enhancement, and intraplaque hemorrhage (IPH). These characteristics are associated with an increased risk of ischemic events, sometimes independent of plaque size and degree of luminal stenosis.^{2,3}

IPH has been the most validated high-risk feature to be associated with accelerated plaque progression and ischemic neurologic events.^{4,5} IPH is thought to be a result of rupture of fragile neovascularization within the plaque.⁶ The accumulation of erythrocyte membranes within the atherosclerotic plaque contribute to the vulnerability of the plaque by increasing the deposition of cholesterol, recruiting macrophages, and increasing the size of the lipid-rich necrotic core.⁷ Careful monitoring of atherosclerotic plaques for the presence and development of IPH would therefore be

valuable in the risk stratification and management of carotid artery disease.

Little, however, remains known about the associations between IPH and various other high-risk plaque features, particularly plaque enhancement. The prior studies that have been performed on this subject have often relied on CTA imaging or histologic analyses following carotid endarterectomy. Additionally, there is scant information in the literature regarding whether the volume of IPH is associated with vulnerable plaque characteristics. This study therefore set out to assess whether IPH and volumetric analyses of IPH signal are associated with other worrisome plaque features on MRA imaging.

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Methods and materials

Study population

This study was completed after obtaining approval from the local Institutional Review Board. A retrospective review was carried out that included patients that underwent MRA of the carotid arteries between 1/1/2016 and 3/31/2021; to be included patients had to have had IPH in at least one of the two carotid arteries. IPH was defined as maximum intralesional intraplaque signal on Magnetization Prepared RAPid Gradient Echo (MPRAGE) images $\geq 200\%$ of the adjacent sternocleidomastoid muscle. A single neuroradiologist reviewer assessed each MRI for quality; examinations were excluded if the image was of poor quality or affected by artifact ($n = 1$) or if large intraluminal thrombi were present ($n = 2$).

MR imaging protocol

Carotid MRA was performed on a 3T MRI scanner (GE 750, GE Healthcare, Milwaukee, WI) with a 16-channel head/neck/spin (HNS) coil. A 3D MPRAGE sequence was obtained for all patients (TR = 13.2 ms, TE = 3.2 ms, flip angle = 15° , slice thickness = 1 mm, number of excitations = 2, TI = 304 ms, in plane spatial resolution = $0.63 \text{ mm} \times 0.63 \text{ mm}$, and acquisition time 3 min 50 s). 2D time of flight (TOF) and gadolinium bolus carotid imaging in the coronal plane were also obtained. In most patients, pre- and post-Gd T1 fat-saturated CUBE imaging in the coronal plane was also performed to examine for the presence of a lipid-rich necrotic core (LRNC) and plaque enhancement.

Image analysis

Each MRA examination was reviewed by a single blinded board-certified neuroradiologist. Each of the studies were assessed for the presence or absence of IPH, defined as maximum intralesional signal intensity (SI) $\geq 200\%$ of the adjacent sternocleidomastoid muscle (Figure 1).⁸ The volume of each carotid artery IPH, if present, was obtained by manually outlining the region of interest in the institution's PACS system (Visage, Visage Imaging Inc., San Diego, CA).

All carotid artery plaques were assessed for the presence of other high-risk characteristics, including IPH, plaque ulceration, plaque enhancement, and LRNC. Plaques were considered to have an LRNC (Figure 1) if there was a slightly hyperintense signal on pre-Gd T1 CUBE images without superimposed IPH. Ulcerations were defined as the presence of outpouchings that were at least 2 mm in depth of the vessel lumen into the carotid plaque lesion.⁹ This study looked at central plaque enhancement (Figure 2), defined as enhancement that is centrally-located within the plaque.¹⁰ Enhancement of the fibrous cap and/or vascular intima was not considered pathologic. Images were not examined for the presence or absence of LRNC or plaque enhancement if pre- and post-contrast T1 CUBE images were not obtained, respectively.

Statistical analysis

Means and standard deviations (STDs) were calculated for all continuous variables. BlueSky Statistics (BlueSky Statistics

LLC, Chicago, IL, USA) software was used to perform statistical calculations. A chi-squared test was used to calculate differences between categorical variables. p -values below .05 were considered statistically significant. A student's t test was used to assess for associations between plaque features and volumetric analyses.

Results

A total of 102 patients were included in the final patient cohort, with a total of 204 ICAs available for analysis. The mean age for the cohort was 73.5 (SD = 9.0). 88 (86.3%) of the patients were male. Characteristics of the patients imaged are summarized in Table 1. Characteristics of right and left ICAs are shown in Table 2.

Both IPH and LRNC were more commonly seen in the left carotid artery ($p = .018$ and $p = .047$, respectively). However, the difference in volume of IPH between the left and right side was not statistically significant ($p = .37$). There was also no difference between right and left carotid arteries in terms of presence of plaque ulceration ($p = .14$) or plaque enhancement ($p = .49$).

On the right side, there was a significant association between the presence of LRNC and IPH ($p < .0001$). Plaque ulceration was present in 11/48 (22.9%) of plaques with IPH and in 5/54 (9.3%) of plaques without IPH (Table 3), with no statistical difference between groups ($p = .06$). No significant difference was noted in IPH volumes in plaques without an ulcer ($184.4 \text{ mm}^3 \pm 133.2$) than those with an ulcer ($139.0 \text{ mm}^3 \pm 141.6$) ($p = .33$). Lesions without IPH were more likely to have plaque enhancement than those with IPH 8/47 (17.0%) versus 1/35 (2.8%), respectively; ($p = .04$). IPH volume could not be statistically assessed in terms of its relationship to enhancement or LRNC since only one artery demonstrated both attributes.

On the left side, there was a significant association between the presence of IPH and LRNC ($p < .0001$), though the presence of LRNC was not associated with differences in IPH volume ($p = .37$). Plaque ulceration was noted in 5/23 (15.6%) of plaques with IPH, and in 20/70 (28.6%) of plaques without IPH, with no significant differences between groups ($p = .16$) (Table 4). Lesions without an ulcer had very similar IPH volumes ($186.3 \text{ mm}^3 \pm 191.0$) compared to those with an ulcer ($188.7 \text{ mm}^3 \pm 220.3$ with) ($p = .96$). No significant difference was noted in the incidence of enhancement between plaques without IPH (4/27; 14.8%) and those with IPH (8/48; 16.7%) ($p = .94$). Similarly, no significant difference was noted in the IPH volume of plaques that demonstrated enhancement ($166.8 \text{ mm}^3 \pm 110.3$) compared to those without enhancement ($218.8 \text{ mm}^3 \pm 224.6$) ($p = .53$) (Table 5).

Discussion

This study sought to assess the relationship between carotid plaque IPH and other high-risk plaque components – namely the presence or absence of ulceration, LRNC, and/or pathologic enhancement. The results found significant overlap between the presence of IPH and LRNC. There is evidence that atherosclerotic plaques that lacked enhancement were more likely to have IPH (only noted on the right side). IPH



Figure 1. Examples of lipid-rich necrotic core (LRNC) and intraplaque hemorrhage (IPH). A plaque in the proximal left ICA (curved arrow, A), demonstrates slightly increased T1 signal on axial-reformatted pre-gad T1 CUBE images (between straight arrows, B). On axial-reformatted MPRAGE images, part-but not all-of this region demonstrates markedly increased signal, compatible with IPH (black asterisk, C). White asterisks denote the vessel lumen in B and C.

volume, conversely, was not associated with any other plaque component, suggesting that these features may not play a role in the severity/volume of hemorrhage.

The noted association between LRNC and IPH is expected, as IPH is typically superimposed on a histologic backdrop of LRNC. Previous studies have demonstrated significant associations between the presence of IPH and LRNC. A histopathologic study carried out by Derksen et al. examined carotid endarterectomy specimens and found that IPH was associated with large lipid cores.¹¹ Hishikawa et al. also found that IPH was strongly associated with LRNC in patients with high-grade carotid artery stenosis. Furthermore, they also found that higher IPH scores (which they defined as plaques with higher ratios of glycoporphin A to total plaque area) were significantly associated with larger necrotic cores, with some evidence that IPH could contribute to expansion of the LRNC.¹² Similarly, Takaya et al. assessed the role of IPH in progression of atherosclerotic plaques and found that plaques with IPH were more likely to have an increase in overall wall

volume and LRNC volume over 18 months.¹³ These findings align with results of a study done by Kolodgie et al. that found that IPH may be a potent atherogenic stimulus contributing to the growth of lipid-rich necrotic cores.⁷

The inverse correlation between the presence of IPH and enhancement was surprising. In general, high-risk plaque features are thought to be associated with one another, as they all represent features of atherosclerotic vulnerability. Plaque enhancement, specifically, is a marker of neovascularization, inflammation, and loose matrix composition, all of which are known characteristics of unstable plaques.¹⁴ Millon et al. found no association between plaque enhancement and IPH, though those authors included various types of enhancement including that of the fibrous cap.¹⁰ It is possible that the results of the current study are related to the intrinsic T1 hyperintense signal present in the setting of IPH. Such signal could mask underlying enhancement by increasing the pre-contrast T1 intensity of the plaque, and thus making it falsely appear as though a negative correlation between IPH and enhancement

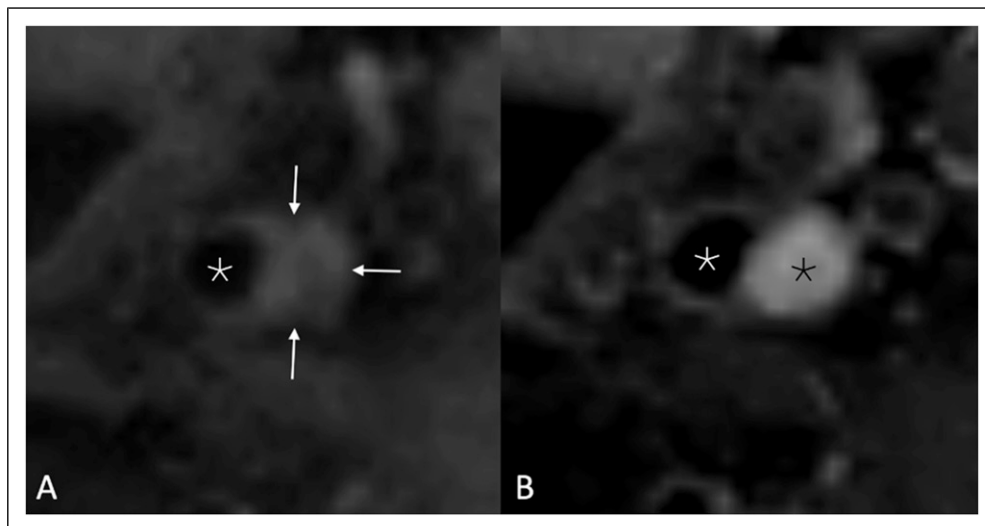


Figure 2. Example of pathologic enhancement of a plaque. Axial reformatted pre-(A) and post-gadolinium (B) T1 CUBE fat-saturated images demonstrate a large lipid-rich necrotic core (LRNC) in an atherosclerotic plaque in the proximal left ICA (between straight arrows, A). This LRNC demonstrates homogeneous enhancement on post-contrast images (black asterisk, B). White asterisks denote the vessel lumen.

Table 1. Baseline characteristics of patients imaged.

Age (mean)	73.5 yrs
Gender (n, %)	Male: 88 (86%) Female: 14 (14%)
HTN (n, %)	78 (76%)
Hyperlipidemia (n, %)	91 (89%)
Diabetes mellitus (n, %)	34 (33%)
Atrial fibrillation (n, %)	16 (16%)
Smoking status (n, %)	Never smoker: 43 (42%) Current smoker: 9 (9%) Former smoker: 50 (49%)
Medication use at time of imaging (n, %)	
a. Plavix	a. 39 (38%)
b. Statin	b. 88 (86%)

Table 2. Features of high-risk plaques found in right and left internal carotid arteries.

	Right ICA	Left RCA	p-value
IPH	48 (47.1%)	70 (68.6%)	.018
LRNC	53 (52.0%)	65 (64.7%)	.047
Ulceration	16 (15.7%)	25 (24.5%)	.014
Enhancement	8 (7.8%)	11 (10.8%)	.49

exists, as was noted in the current study. The data of the current study must therefore be interpreted cautiously.

Although the current study failed to find a correlation between IPH and ulceration, this association has been well-established previously. Dilba et al., in the most comparable prior study, assessed whether certain plaque features were associated with atherosclerotic ulceration.¹⁵ The authors found that plaque ulcers were associated with larger vessel wall volumes, as well as volumes of both LRNC and IPH. Ulcers were not, however, found to be associated with the presence of IPH ($p = .61$). U-King-Im et al., similarly, found that plaque ulceration had strong sensitivity and specificity

Table 3. IPH relationship with plaque ulceration in left- and right-sided carotid plaques.

	Plaque ulceration IPH + (n; %)	Plaque ulceration – (n; %)	Total (n)	p-value
Left +	20 (28.6%)	50 (71.4%)	70	.16
Left –	5 (15.6%)	27 (84.4%)	32	
Right +	11 (22.9%)	37 (77.1%)	48	.06
Right –	5 (9.3%)	49 (90.7%)	54	

for predicting IPH, and offered it as a surrogate marker for IPH on CTA imaging.³ Lovett et al. found an association between ulceration on CTA and IPH and a large LRNC on subsequent endarterectomy samples.¹⁶

This study has similar limitations to other retrospective studies. Furthermore, this study did not set out to assess the relationship between the co-occurrence of carotid plaque ulceration, enhancement, LRNC, and IPH with cerebrovascular events. Therefore, the clinical symptoms of these vulnerable plaque characteristics if/when they occur concomitantly is not known. The study is also limited by the sensitivity of MRA for plaque ulceration, as CTA is considered to be the best imaging modality to define the presence/absence of plaque ulceration (with a sensitivity of 94% compared to the 82% sensitivity of MRA).^{17,18} Next, the cohort in this study is made up exclusively of patients with IPH in at least one of their carotid arteries. As such, selection bias may have affected some of the observed results. Finally, as stated above, T1 hyperintense signal intrinsic to IPH could have obscured the observation of enhancement in some plaques. This limitation could potentially be overcome by using subtracted imaging between the post-Gd and pre-Gd images. In this study we did not have the sequences needed to perform subtraction, but this would be a way to solve this potentially technical issue in future studies. Future studies could also benefit from histologic confirmation of findings to assess for associations between IPH and various other plaque markers. Ideally, prospective studies with longitudinal

Table 4. IPH relationship with plaque enhancement in left and right-sided carotid plaques.

		Enhancement + IPH (n; %)	Enhancement – (n; %)	Total (n)	p-value
Left	+	8 (16.7%)	40 (83.3%)	48	.94
	–	4 (14.8%)	23 (85.2%)	27	
Right	+	1 (2.8%)	34 (97.2%)	35	.04
	–	8 (17.0%)	39 (83.0%)	47	

Table 5. Plaque ulceration and enhancement relationship with volume of IPH in left and right-sided carotid plaques. Association between IPH volume and enhancement was not assessed on the right side due to n = 1 with both attributes.

	Plaque features	IPH volume	p-value
Left	Ulceration +	188.7 ± 220.3	.96
	Ulceration –	186.3 ± 191.0	
	Enhancement +	166.8 ± 110.3	
	Enhancement –	218.8 ± 224.6	
Right	Ulceration +	139.0 ± 141.6	.33
	Ulceration –	184.4 ± 133.2	
	Enhancement +	–	
	Enhancement –	–	

imaging evaluation would provide useful data regarding the temporal relationship between these plaque features.

Also notable is that the study sample size is relatively small and heterogeneous in age and relatively unbalanced in gender. This is important to consider as the incidence and severity of atherosclerosis is greater in men compared to women across all age groups.¹⁹ Differences in incidence of cardiovascular disease are also influenced by gender differences in cardiovascular risk factors and disease presentation.²⁰ Furthermore, differences in findings of plaque characteristics and associations between these characteristics were found between right and left carotid arteries. The underlying mechanism of these differences remains unclear and provides an avenue for future studies.

In conclusion, this study found a significant association between IPH and LRNC. An unexpected inverse correlation was noted between the presence of IPH and plaque enhancement, which is possibly due to the intrinsic hyperintense T1 signal in hemorrhage plaques. No associations were found between IPH and ulceration, nor were associations found between the volume of IPH and any other the other high-risk plaque features. It is possible that the study was underpowered and therefore not able to find a correlation. Together, these findings indicate that while some high-risk plaque markers are associated with IPH, they seem to play little role in the volume of plaque hemorrhage.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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