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Ipsilateral plaques display higher T1 signals than contralateral plaques in recently symptomatic patients with bilateral carotid intraplaque hemorrhage

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Abstract

Background and aims—Prospective studies have shown a strong association between carotid intraplaque hemorrhage (IPH), detected by magnetic resonance imaging (MRI), and cerebrovascular ischemic events. However, IPH is also observed in a substantial number of asymptomatic patients. We hypothesized that there are differences in the characteristics of IPH+ plaques associated with recent symptoms, compared to IPH+ plaques not associated with recent symptoms.

Methods—Patients with recent (< 2 weeks) anterior circulation ischemic events were scanned using a standardized multisequence protocol. Those showing IPH bilaterally were included and analyzed for differences in T1/T2 signals, plaque morphology, and coexisting plaque characteristics between the ipsilateral symptomatic and contralateral asymptomatic sides.

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Conflict of interest

All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Author contributions

Literature search: XW, JS. Study conception and design: JS, TSH, CY. Study implementation: XZ, JL, RL, YS. Data collection: XW, JS, XZ, GC, YS. Statistical analysis: JS, DSH. Data interpretation: all authors. Manuscript preparation: XW, JS, XZ. Manuscript revision: all authors.

Results—Thirty-one subjects (67 ± 9 years, 97% males) with bilateral IPH were studied. Despite comparable luminal stenosis ($53\pm 42\%$ vs. $53\pm 39\%$, $p=0.99$), T1 signal of IPH measured as signal-intensity-ratio compared to muscle was stronger ($SIR_{IPH\text{-to-muscle}}$: 5.8 ± 2.4 vs. 4.7 ± 1.8 , $p=0.004$) and tended to be more extensively distributed (IPH volume: 150 ± 199 vs. 88 ± 106 mm³, $p=0.071$) on the symptomatic side. IPH+ plaques on the symptomatic side were longer (24 ± 6 vs. 21 ± 7 mm, $p=0.026$) and associated with larger necrotic core volume (406 ± 354 vs. 291 ± 293 mm³, $p=0.039$) than those on the asymptomatic side.

Conclusions—In recently symptomatic patients with bilateral carotid IPH, the symptomatic side showed stronger T1 signals, larger necrotic cores, and longer plaque length than the asymptomatic side. Serial studies on the temporal relationship between these imaging features and clinical events will eventually establish their diagnostic and prognostic value beyond the mere presence of IPH.

Keywords

carotid artery; magnetic resonance imaging; ischemic stroke; plaque progression

1. Introduction

Intraplaque hemorrhage (IPH) has been recognized as a hallmark feature of high-risk carotid atherosclerosis, with accumulative evidence from histopathological studies as well as natural history studies using *in vivo* magnetic resonance imaging (MRI) [1–6]. Recent meta-analyses of prospective carotid MRI studies have demonstrated a strong association between IPH and increased risk of cerebrovascular ischemic events [7–9].

However, IPH has also been detected in a substantial number of asymptomatic patients who have never experienced ischemic neurological symptoms [10,11]. Furthermore, serial studies with carotid MRI observed that IPH can occur silently and persist for years without causing clinical symptoms [12]. As such, identifying the mere presence of IPH may be insufficient to precisely identify the patient at greater risk for cerebrovascular ischemic events. The mechanisms linking the onset of IPH and subsequent ischemic events remain incompletely understood.

Highly T1-weighted sequences such as magnetization-prepared rapid acquisition gradient echo (MPRAGE) have been shown to detect carotid IPH with high sensitivity and specificity [13,14], whereas a multisequence protocol including time-of-flight (TOF) and turbo spin echoes has been shown to provide a detailed assessment of plaque characteristics [15,16]. In recently symptomatic patients with bilateral carotid IPH, this study sought to examine whether there are differences in the characteristics of IPH+ plaques associated with recent symptoms, compared to IPH+ plaques not associated with recent symptoms.

2. Patients and methods

2.1. Study sample

The Carotid Atherosclerosis Risk Assessment (CARE-II) study is an ongoing multicenter carotid MRI study (NCT02017756) in Chinese patients with recent cerebrovascular ischemic events, which aims to determine the prevalence and characteristics of high-risk carotid

disease in a geographically diverse symptomatic population in China. Subjects were recruited from stroke clinics at 13 participating hospitals with the following inclusion criteria: 1) 18–80 years old males and females; 2) anterior circulation cerebrovascular ischemic events (ischemic stroke, transient ischemic attack, or amaurosis fugax) within the past two weeks; and 3) presence of carotid plaque (focal intima-media thickness ≥ 1.5 mm) on carotid ultrasound. Those with cardioembolic stroke, history of radiation therapy to the neck, or contraindications to MRI examination were excluded. For the present study, CARE-II subjects were screened to identify those showing bilateral carotid IPH on MPRAGE (see 2.3 Image Review for details). Patient demographics and clinical characteristics were collected by the referring physicians. Luminal stenosis was measured by radiologists on TOF MR angiography using the NASCET criteria [17]. Institutional review board approval was obtained at each participating institution. Study participants provided written informed consent.

2.2. Multisequence carotid MRI

Subject scans were performed on 3T clinical scanners (Achieva TX, Philips Healthcare, Best, the Netherlands) with dedicated eight-channel carotid coils (Chenguang Medical Technologies, Shanghai, China). A standardized multisequence protocol was used [18,19], including three-dimensional TOF, MPRAGE, and black-blood T1-weighted (T1W) and T2-weighted (T2W) turbo spin echoes. All images were acquired in the axial plane, with field-of-view of 160×160 mm², matrix of 256×256 , and slice thickness of 2 mm. In-plane resolution was 0.625×0.625 mm² acquired and 0.31×0.31 mm² interpolated. Inter-slice spacing was 0 mm in T1W/T2W and -1 mm (1 mm overlap) in TOF/MPRAGE. Scan coverage was 32 mm in T1W/T2W and 48 mm in TOF/MPRAGE. Additional details regarding MRI sequence parameters can be found in the technical paper published previously [19].

2.3. Image review

Measurements on plaque morphology and characteristics were performed in a core lab (Vascular Imaging Lab, University of Washington, Seattle, USA) by trained readers using a custom-designed image analysis software package (CASCADE, University of Washington, Seattle, USA) and a previously described multicontrast review approach [3,10,11,15,16]. Interreader and interscan reproducibility of multicontrast review using CASCADE have been previously evaluated [18,20,21]. In this study, each case was reviewed by the same two readers who were blinded to the subjects' clinical information, and their consensus interpretation of the images were recorded. Cases with disagreement after discussion between the two readers were adjudicated by a third reader.

Briefly, using the flow divider of the common carotid artery bifurcation as a landmark, axial series were aligned and registered. Inner and outer boundaries of artery wall and plaque components, including calcification, lipid-rich necrotic core (LRNC), and IPH were manually outlined. Using adjacent muscle and normal wall segment as reference, calcification was determined as hypointense areas on all contrast weightings. Non-calcified hypointense areas on T2W were classified as LRNC regions (Fig. 1 and 2). IPH was identified as hyperintense areas on MPRAGE (Fig. 1 and 2). Thin/ruptured fibrous cap was

recorded if a portion of the fibrous cap was not visualized on T2W/TOF with or without surface irregularity (Fig. 1). Surface ulceration was identified as distinct surface depressions with similar signals to the flowing blood (Fig. 2). Mural thrombus was recorded if there were distinct filling defects in lumen or T2 hyperintensities (indicating organizing thrombi) on the surface associated surface disruption (Supplemental Fig. 2). Maximum and mean wall thickness, maximum percent wall area ($100\% \times [\text{wall area} / \text{total vessel area}]$), and percent wall volume ($100\% \times [\text{wall volume} / \text{total vessel volume}]$) were calculated from image segmentation results. Plaque length was defined as the number of slices with distinct plaque (maximum wall thickness ≥ 1.5 mm) multiplied by slice thickness. Previous studies indicate that IPH+ plaques are longer than IPH- plaques and frequently extend across the flow divider of the common carotid artery [22]. Therefore, plaque location was recorded as above or below the flow divider by comparing the slice with largest plaque burden (maximum percent wall area) relative to the flow divider.

Measurements on IPH signal characteristics, including longitudinal length (number of slices with IPH multiplied by slice thickness), maximum IPH area, and IPH volume were also derived from image segmentation in CASCADE. T2 signal intensity was recorded qualitatively by comparing to sternocleidomastoid muscle. T1 signal intensity was measured quantitatively on MPRAGE using a standard DICOM viewer (RadiAnt, Medixant, Poznan, Poland). Regions-of-interest were drawn to enclose the wall area on each axial MPRAGE image, of which the maximum signal intensity was recorded and normalized to sternocleidomastoid muscle as signal-intensity-ratio ($\text{SIR}_{\text{IPH-to-muscle}}$: signal intensity of IPH / signal intensity of muscle).

2.4. Statistical analysis

Continuous variables were summarized as mean $\pm$ standard deviation (SD) or range, and binary variables were summarized as count (percentage). All included subjects had bilateral carotid IPH and unilateral ischemic symptoms, so plaques were grouped by whether they were ipsilateral or contralateral to the ischemic symptoms. Differences between ipsilateral and contralateral IPH+ plaques were then assessed using the paired t-test for continuous variables and the Sign test for binary variables. Associations between the symptomatic and asymptomatic sides were assessed using the Spearman's rank correlation coefficient for continuous variables and odds ratios for binary variables. All statistical calculations were conducted with the statistical computing language R (version 3.1.1; R Foundation for Statistical Computing, Vienna, Austria). Throughout, two-sided tests were used with statistical significance defined as $p < 0.05$.

3. Results

3.1. Clinical characteristics

Of 582 recently symptomatic subjects screened, 49 (8.4%) were deemed to have poor image quality, insufficient scan coverage, too much tortuosity, or total occlusion that affected at least one side of carotid arteries. Thirty-one (5.8%) of the 533 remaining subjects were identified as having bilateral carotid IPH. Symptomatic plaques were on the left side in 17 cases and on the right side in 14 cases. Clinical characteristics are summarized in Table 1.

Seventeen (54.8%) subjects were recruited because of ischemic stroke. Nearly all subjects were male (96.8%), with a mean age of 67 ± 9 years (range: 43 – 83 years). The prevalence of smokers (former or current) and those with hypertension, and hyperlipidemia were 67.7%, 87.1%, and 77.4%, respectively. Notably, 45.2% of the subjects were diabetic.

3.2. Plaque location and luminal stenosis

In most plaques, largest plaque burden measured as maximum percent wall area was observed at/above the flow divider (symptomatic vs. asymptomatic: 83.9% vs. 80.6%, $p=0.99$) (Table 2). The location of bilateral carotid plaques relative to the flow divider were correlated ($p=0.038$). IPH+ plaques on the symptomatic and asymptomatic side showed a similar degree of luminal stenosis ($53 \pm 42\%$ vs. $53 \pm 39\%$, $p=0.99$). There was a significant correlation between the two sides on degree of stenosis (Spearman's $\rho=0.51$, $p=0.006$).

3.3. IPH signal characteristics

Measures of IPH size and T1 signal intensity were moderately correlated between the symptomatic and asymptomatic side ($p<0.05$ for all; Table 2). However, compared with the asymptomatic side, the normalized maximum T1 signal intensity ($SIR_{IPH-to-muscle}$) was significantly greater on the symptomatic side (5.8 ± 2.4 vs. 4.7 ± 1.8 , $p=0.004$) (Fig. 1 and 3). This was accompanied by a trend toward a higher IPH volume (150 ± 199 vs. 88 ± 106 mm³, $p=0.071$) on the symptomatic side (Table 2; Supplemental Figure 1). Among all the arteries, maximum IPH signal intensity and IPH volume demonstrated a positive correlation (Spearman's $\rho=0.57$, $p<0.001$). T2 signal intensity did not differ significantly between the two sides ($p>0.99$).

3.4. Plaque morphology

Plaque length was significantly greater (24 ± 6 vs. 21 ± 7 mm, $p=0.026$) and focal plaque burden measured as maximum percent wall area tended to be larger ($77 \pm 12\%$ vs. $73 \pm 11\%$, $p=0.071$) on the symptomatic side. Other plaque burden measurements including maximum wall thickness (5.3 ± 1.6 vs. 4.7 ± 1.7 mm, $p=0.11$), mean wall thickness (2.1 ± 0.5 vs. 2.0 ± 0.5 mm, $p=0.43$), and percent wall volume ($60 \pm 8\%$ vs. $59 \pm 9\%$, $p=0.62$) were not significantly different between the two sides.

3.5. Coexisting plaque characteristics

Coexisting plaque characteristics were generally similar between the symptomatic and asymptomatic side, except that the symptomatic side had larger lipid-rich necrotic core volume (406 ± 354 vs. 291 ± 293 mm³, $p=0.039$) and a trend towards a higher prevalence of mural thrombus (29.0% vs. 9.7% , $p=0.11$). The prevalence of thin/ruptured fibrous cap (77.4% vs. 67.7% , $p=0.55$) and surface ulceration (41.9% vs. 32.3% , $p=0.55$) were high on both sides (Table 2; Fig. 1 and 2).

4. Discussion

Despite carotid IPH being strongly associated with cerebrovascular ischemic events, substantial heterogeneity exists among IPH+ plaques in terms of clinical outcomes. The mechanisms linking IPH and clinical events remain poorly understood. To our knowledge,

this is the first study to compare IPH+ plaques associated with recent neurological symptoms to IPH+ plaques not associated with recent symptoms. Differences were observed in quantitative measurements of IPH signals on T1w images as well as in plaque burden and LRNC volume. These data would be not only useful in understanding the pathophysiological mechanisms through which IPH facilitates the transition from asymptomatic to symptomatic plaques, but also informative for pursuing additional imaging markers that could contribute to a more accurate assessment of clinical risk beyond the mere presence of IPH.

In symptomatic patients with bilateral carotid intraplaque hemorrhage, IPH+ plaques demonstrated advanced features whether or not they were ipsilateral to recent cerebrovascular ischemic events. Maximum percent wall area was greater than 70%, and percent wall volume was $\approx 60\%$ on the symptomatic and asymptomatic sides. The prevalence of thin/ruptured fibrous cap was as high as 70% on both sides. Therefore, even though subjects in this study were unilaterally symptomatic, there is evidence of notable plaque progression on the asymptomatic side as well. One possible explanation is that the plaques contralateral to clinical symptoms also contained IPH, which has previously been shown to strongly promote plaque progression [12,23,24]. Additionally, there are a number of systemic risk factors related to genetics, lifestyle, and environment that could exert promoting effects on bilateral atherosclerosis. This highlights the strength of the paired study design where each subject serves as his or her own control. As such, the differences between IPH+ plaques ipsilateral and contralateral to clinical symptoms are more likely to reflect their pathophysiological associations with clinical events without being confounded by other systemic factors that could be a concern in comparing different subject groups.

A notable difference between IPH+ plaques ipsilateral and contralateral to clinical symptoms was in IPH signal intensity on heavily T1w images. Maximum $SIR_{IPH-to-muscle}$ and IPH volume measured on MPRAGE represent the strength and extent of IPH signals on T1w images. As the T1-shortening effect associated with IPH is attributable to methemoglobin from erythrocyte degradation [25,26], a stronger T1 signal likely means a higher concentration of methemoglobin locally within the plaque. Other paramagnetic substances, such as ferritin and hemosiderin, do not increase T1 relaxivity because the paramagnetic iron in these forms is inaccessible to water molecules, preventing dipole-dipole interactions [26]. This suggests that IPH on the symptomatic side occurred more frequently, in larger amount, or temporally closer to the clinical event than the asymptomatic side. Elucidating the exact mechanisms relies on serial studies that quantitatively characterize IPH signals over time. Previous studies showed that T1 signals of IPH can persist for years [12,23,27], which may be because methemoglobin from IPH can be trapped in necrotic cores and difficult to clear through the haptoglobin- and hemopexin-mediated pathways [2,28]. If increases in T1 signal are a progressive process that increases the risk of clinical events, quantitative measures of IPH signals may provide sensitive markers of repeated, accumulative IPH in asymptomatic patients. Highly active IPH+ plaques can be identified with imaging follow-up, presenting a treatment window for stroke prevention. Alternatively, increases in T1 signals may occur almost simultaneously with clinical events as an indicator of acute IPH, which could be the trigger (blood extravasation from vasa vasorum) or consequence (blood infiltration from the lumen side) of acute plaque rupture. In

this scenario, increases in T1 signals may be used for identifying culprit lesions in symptomatic patients.

Compared to T1 signal intensity, T2 signal intensity of IPH has been less studied because of unclear clinical implications. Hemorrhages in other tissues have a predictable time course of days to months on MRI [26]. However, serial studies of IPH showed that its T2 signal intensity appeared to be quite persistent [23], which again may be related to the unique intraplaque environment. The catabolism and repairing processes following hemorrhages that take place in other tissues may not function well within atherosclerotic plaques. Whether quantitative measures of T2 signal intensity through T2 mapping may provide more sensitive information of IPH signal evolution remains to be investigated in future studies.

Interestingly, there was a moderate correlation in T1 signals between bilateral IPH+ plaques, suggesting that repeated IPH, as a determinant of the magnitude and extent of T1 signals, is influenced by systemic factors. Vasa vasorum proliferation, which is considered as a major source for IPH [29–31], has been shown to be a systemic feature in patients with symptomatic atherosclerosis [32]. Haptoglobin genotype, which is considered to lead to different tissue responses to IPH, was found to be associated with iron deposition in atherosclerotic plaques [33]. Furthermore, blood pressure fluctuation was recently indicated as an unrecognized risk factor in the pathogenesis of IPH [22,34]. These traditional and novel risk factors could have unique influences on the natural history of IPH+ plaques that is different from their effects on IPH-plaques. Quantitative measures of T1 signal characteristics may provide an opportunity to further investigate the role of systemic risk factors in the development and progression of IPH.

Besides T1 signals of IPH, other differences between symptomatic and asymptomatic IPH+ plaques were noted in plaque length and LRNC volume. Large LRNC on ultrasound or MRI has long been recognized as a marker of increased stroke risk [3,35] whereas previous data linking carotid plaque length and stroke risk have been scarce. Conceivably, increased plaque length and LRNC volume present a larger fibrous cap area that is at risk of rupture. As a hypothesis-generating study, we did not adjust for multiple comparisons. Nonetheless, the significant findings do not appear random but point to a unifying mechanism. One possible mechanism is that these differences in plaque morphology and coexisting plaque characteristics may be the outcomes of plaque progression driven by repeated IPH. IPH has been found to be associated with rapid plaque progression, characterized by a decrease in lumen area and an increase in LRNC volume [23,24,36]. Accordingly, plaques with more accumulative IPH are likely to be associated with longer length and larger LRNC. Alternatively, plaques with longer length and larger LRNC may be more likely to cause acute plaque rupture and thus acute IPH. Thin/ruptured fibrous cap and surface ulceration were frequently seen in IPH+ plaques irrespective of being ipsilateral or contralateral to clinical symptoms. This finding suggests that plaque surface disruption can be commonly present in symptomatic patients and is not necessarily associated with ipsilateral symptoms. Similarly, a previous histopathological study showed that the prevalence of ulceration was comparable for carotid plaques associated with ipsilateral and contralateral symptoms [37].

This hypothesis-generating study is limited by the small sample size. However, the study population is quite unique and has been rarely described in previous studies. The within-subject comparison, using the contralateral IPH+ plaque as a matched control, mitigated potential confounding by systemic factors. Second, this is a cross-sectional study with assessment of plaque characteristics at a single time point. It is unknown whether increases in T1 signals proceed (as the trigger) or follow (as the consequence) clinical symptoms. Serial imaging studies will be needed to further characterize the evolution of IPH and its relationship with clinical events. Subacute mural thrombi may also display high T1 signals but are less commonly seen in the carotid artery compared to IPH [38]. This is probably because nonocclusive arterial thrombi are often not rich in erythrocytes. Additionally, iron catabolism in mural thrombi is likely different from that in IPH. Methemoglobin can be readily phagocytosed in mural thrombi, preventing its accumulation (and strengthened T1 relaxivity effects). Per study objective, specific attention was paid to excluding mural thrombi in measuring IPH signal intensity. The strongest signal was always measured from within the plaque. Therefore, the observed difference in T1 signal is unlikely attributed to mural thrombi. Nonetheless, there was no histopathological data in this study to confirm the exact source of T1 signals. Finally, although subjects were recruited in a multicenter study, T1 signal measurements were performed on a single platform using a unified MRI protocol. Further studies using similar but not identical techniques are needed. Despite these limitations, this study has revealed important differences between symptomatic and asymptomatic IPH+ plaques and highlighted the opportunities for understanding the biology of IPH using quantitative measures of T1 signals. Ultimately, a T1 mapping technique to provide absolute quantification is desired to establish IPH T1 signals as an imaging biomarker to monitor plaque progression in the clinical setting.

In conclusion, despite similar plaque location and luminal stenosis, IPH+ plaques ipsilateral to clinical symptoms demonstrated stronger T1 signals, longer plaque length and larger LRNC volume than those contralateral to clinical symptoms in recently symptomatic patients with bilateral carotid IPH. Quantitative characterization of IPH signals on MRI may be an informative novel imaging marker in future prospective serial studies to further our understanding of the pathophysiological role that IPH plays in clinical symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Kolodgie FD, Gold HK, Burke AP, et al. Intraplaque hemorrhage and progression of coronary atheroma. *N Engl J Med*. 2003; 349:2316–2325. [PubMed: 14668457]
2. Nagy E, Eaton JW, Jeney V, et al. Red cells, hemoglobin, heme, iron, and atherogenesis. *Arterioscler Thromb Vasc Biol*. 2010; 30:1347–1353. [PubMed: 20378845]
3. Takaya N, Yuan C, Chu BC, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI - initial results. *Stroke*. 2006; 37:818–823. [PubMed: 16469957]
4. Altaf N, Daniels L, Morgan PS, et al. Detection of intraplaque hemorrhage by magnetic resonance imaging in symptomatic patients with mild to moderate carotid stenosis predicts recurrent neurological events. *J Vasc Surg*. 2008; 47:337–342. [PubMed: 18164171]
5. Singh N, Moody AR, Gladstone DJ, et al. Moderate carotid artery stenosis: MR imaging-depicted intraplaque hemorrhage predicts risk of cerebrovascular ischemic events in asymptomatic men. *Radiology*. 2009; 252:502–508. [PubMed: 19508983]
6. Kwee RM, van Oostenbrugge RJ, Mess WH, et al. MRI of carotid atherosclerosis to identify TIA and stroke patients who are at risk of a recurrence. *J Magn Reson Imaging*. 2013; 37:1189–1194. [PubMed: 23166040]
7. Hosseini AA, Kandiyil N, Macsweeney ST, Altaf N, Auer DP. Carotid plaque hemorrhage on magnetic resonance imaging strongly predicts recurrent ischemia and stroke. *Ann Neurol*. 2013; 73:774–784. [PubMed: 23463579]
8. Gupta A, Baradaran H, Schweitzer AD, et al. Carotid Plaque MRI and Stroke Risk: A Systematic Review and Meta-analysis. *Stroke*. 2013; 44:3071–3077. [PubMed: 23988640]
9. Saam T, Hetterich H, Hoffmann V, et al. Meta-analysis and systematic review of the predictive value of carotid plaque hemorrhage on cerebrovascular events by magnetic resonance imaging. *J Am Coll Cardiol*. 2013; 62:1081–1091. [PubMed: 23850912]
10. Saam T, Underhill HR, Chu BC, et al. Prevalence of American heart association type VI carotid atherosclerotic lesions identified by magnetic resonance imaging for different levels of stenosis as measured by duplex ultrasound. *J Am Coll Cardiol*. 2008; 51:1014–1021. [PubMed: 18325441]
11. Zhao X, Underhill HR, Zhao Q, et al. Discriminating Carotid Atherosclerotic Lesion Severity by Luminal Stenosis and Plaque Burden: A Comparison Utilizing High-Resolution Magnetic Resonance Imaging at 3.0 Tesla. *Stroke*. 2011; 42:347–353. [PubMed: 21183749]
12. Sun J, Underhill HR, Hippe DS, Xue Y, Yuan C, Hatsukami TS. Sustained acceleration in carotid atherosclerotic plaque progression with intraplaque hemorrhage: a long-term time course study. *J Am Coll Cardiol Img*. 2012; 5:798–804.
13. Bitar R, Moody AR, Leung G, et al. *In vivo* 3D high-spatial-resolution MR imaging of intraplaque hemorrhage. *Radiology*. 2008; 249:259–267. [PubMed: 18796681]
14. Ota H, Yarnykh VL, Ferguson MS, et al. Carotid intraplaque hemorrhage imaging at 3.0-T MR imaging: comparison of the diagnostic performance of three T1-weighted sequences. *Radiology*. 2010; 254:551–563. [PubMed: 20093526]
15. Cai JM, Hatsukami TS, Ferguson MS, Small R, Polissar NL, Yuan C. Classification of human carotid atherosclerotic lesions with *in vivo* multicontrast magnetic resonance imaging. *Circulation*. 2002; 106:1368–1373. [PubMed: 12221054]
16. Saam T, Cai J, Ma L, et al. Comparison of symptomatic and asymptomatic atherosclerotic carotid plaque features with *in vivo* MR imaging. *Radiology*. 2006; 240:464–472. [PubMed: 16864672]
17. North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. *Stroke*. 1991; 22:711–720. [PubMed: 2057968]
18. Li F, Yarnykh VL, Hatsukami TS, et al. Scan-rescan reproducibility of carotid atherosclerotic plaque morphology and tissue composition measurements using multicontrast MRI at 3T. *J Magn Reson Imaging*. 2010; 31:168–176. [PubMed: 20027584]
19. Sun J, Zhao XQ, Balu N, et al. Carotid magnetic resonance imaging for monitoring atherosclerotic plaque progression: a multicenter reproducibility study. *Int J Cardiovasc Imaging*. 2015; 31:95–103. [PubMed: 25216871]

20. Takaya N, Cai JM, Ferguson MS, et al. Intra- and interreader reproducibility of magnetic resonance imaging for quantifying the lipid-rich necrotic core is improved with gadolinium contrast enhancement. *J Magn Reson Imaging*. 2006; 24:203–210. [PubMed: 16739123]
21. Saam T, Hatsukami TS, Yarnykh VL, et al. Reader and platform reproducibility for quantitative assessment of carotid atherosclerotic plaque using 1.5T Siemens, Philips, and General Electric scanners. *J Magn Reson Imaging*. 2007; 26:344–352. [PubMed: 17610283]
22. Sun J, Canton G, Balu N, et al. Blood Pressure Is a Major Modifiable Risk Factor Implicated in Pathogenesis of Intraplaque Hemorrhage: An *In vivo* Magnetic Resonance Imaging Study. *Arterioscler Thromb Vasc Biol*. 2016; 36:743–749. [PubMed: 26848155]
23. Takaya N, Yuan C, Chu BC, et al. Presence of intraplaque hemorrhage stimulates progression of carotid atherosclerotic plaques: a high-resolution magnetic resonance imaging study. *Circulation*. 2005; 111:2768–2775. [PubMed: 15911695]
24. Underhill HR, Yuan C, Yarnykh VL, et al. Arterial remodeling in the subclinical carotid artery disease. *J Am Coll Cardiol Img*. 2009; 2:1381–1389.
25. Leung G, Moody AR. MR imaging depicts oxidative stress induced by methemoglobin. *Radiology*. 2010; 257:470–476. [PubMed: 20829533]
26. Atlas, SW. Magnetic resonance imaging of the brain and spine. 4th. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.
27. Simpson RJ, Akwei S, Hosseini AA, MacSweeney ST, Auer DP, Altaf N. MR Imaging-Detected Carotid Plaque Hemorrhage Is Stable for 2 Years and a Marker for Stenosis Progression. *AJNR Am J Neuroradiol*. 2015; 36:1171–1175. [PubMed: 25742988]
28. Levy AP, Levy JE, Kalet-Litman S, et al. Haptoglobin genotype is a determinant of iron, lipid peroxidation, and macrophage accumulation in the atherosclerotic plaque. *Arterioscler Thromb Vasc Biol*. 2007; 27:134–140. [PubMed: 17068284]
29. Virmani R, Kolodgie FD, Burke AP, et al. Atherosclerotic plaque progression and vulnerability to rupture: angiogenesis as a source of intraplaque hemorrhage. *Arterioscler Thromb Vasc Biol*. 2005; 25:2054–2061. [PubMed: 16037567]
30. Sluimer JC, Kolodgie FD, Bijmens A, et al. Thin-walled microvessels in human coronary atherosclerotic plaques show incomplete endothelial junctions relevance of compromised structural integrity for intraplaque microvascular leakage. *J Am Coll Cardiol*. 2009; 53:1517–1527. [PubMed: 19389562]
31. Sun J, Song Y, Chen H, et al. Adventitial perfusion and intraplaque hemorrhage: a dynamic contrast-enhanced MRI study in the carotid artery. *Stroke*. 2013; 44:1031–1036. [PubMed: 23471271]
32. Fleiner M, Kummer M, Mirlacher M, et al. Arterial neovascularization and inflammation in vulnerable patients: early and late signs of symptomatic atherosclerosis. *Circulation*. 2004; 110:2843–2850. [PubMed: 15505090]
33. Moreno PR, Purushothaman KR, Purushothaman M, et al. Haptoglobin genotype is a major determinant of the amount of iron in the human atherosclerotic plaque. *J Am Coll Cardiol*. 2008; 52:1049–1051. [PubMed: 18848136]
34. Selwaness M, van den Bouwhuijsen QJ, Verwoert GC, et al. Blood pressure parameters and carotid intraplaque hemorrhage as measured by magnetic resonance imaging: The Rotterdam Study. *Hypertension*. 2013; 61:76–81. [PubMed: 23213192]
35. Gronholdt ML, Nordestgaard BG, Schroeder TV, Vorstrup S, Sillesen H. Ultrasonic echolucent carotid plaques predict future strokes. *Circulation*. 2001; 104:68–73. [PubMed: 11435340]
36. Sun J, Balu N, Hippe DS, et al. Subclinical carotid atherosclerosis: short-term natural history of lipid-rich necrotic core--a multicenter study with MR imaging. *Radiology*. 2013; 268:61–68. [PubMed: 23513240]
37. Fisher M, Paganini-Hill A, Martin A, et al. Carotid plaque pathology: thrombosis, ulceration, and stroke pathogenesis. *Stroke*. 2005; 36:253–257. [PubMed: 15653581]
38. Moody AR, Murphy RE, Morgan PS, et al. Characterization of complicated carotid plaque with magnetic resonance direct thrombus imaging in patients with cerebral ischemia. *Circulation*. 2003; 107:3047–3052. [PubMed: 12796133]

Highlights

Intraplaque hemorrhage plaques ipsi- and contralateral to clinical event are compared

T1 signal of intraplaque hemorrhage is stronger on the symptomatic side

Plaque length and lipid core size are greater on the symptomatic side

Bilateral T1 signals are correlated, which may be influenced by systemic factors

Fig. 1. Subject with bilateral IPH+ plaques

The slice with the highest T1 signal intensity is shown between the (A) symptomatic and (B) asymptomatic side ($SIR_{IPH-to-muscle}$: 7.9 vs. 5.2). Original and segmented images are shown. Carotid plaques are delineated by lumen (red) and outer wall (azure) contours. Bilateral plaques demonstrate large necrotic core, IPH (red arrows), and thin fibrous cap (yellow arrows). Necrotic core is detected as non-calcified hypointense areas on T2W (yellow contours). IPH is detected as hyperintense areas on MPRAGE (orange contours). Fibrous cap (not contoured) is by definition the region between necrotic core and carotid lumen and considered thin on both sides as it is partially invisible on T2W. MPRAGE indicates

magnetization-prepared rapid acquisition gradient echo; SIR, signal-intensity-ratio; T1W, T1-weighted; T2W, T2-weighted; TOF, time-of-flight.

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Fig. 2. Subject with bilateral ulcerated plaques

Surface ulceration, identified as distinct surface depression (white arrows), is present on both the (A) symptomatic and (B) asymptomatic side. Original and segmented images are shown. Carotid plaques are delineated by lumen (red) and outer wall (azure) contours. Bilateral plaques demonstrate remnant necrotic core (yellow), IPH (orange), and ulceration (violet red). There is also a small calcification (dark blue) on the symptomatic side. Abbreviations as in Fig. 1.

Fig. 3. Differences between IPH+ plaques ipsilateral and contralateral to clinical symptoms
 The symptomatic side demonstrates (A) stronger T1 signals, (B) longer plaque length, and (C) larger lipid core volume than the asymptomatic side. Short horizontal lines on the line charts indicate mean values.

Table 1

Clinical characteristics.

	Mean $\pm$ SD or No. (%)	Range
Qualifying events		
Ischemic stroke	17 (54.8)	
TIA/amaurosis fugax	14 (45.2)	
Age, years	67 $\pm$ 9	43 – 83
Male sex	30 (96.8)	
Body mass index, kg/m ²	25.5 $\pm$ 2.1	19.2 – 28.7
Smoking	21 (67.7)	
Hypertension	27 (87.1)	
Hyperlipidemia	24 (77.4)	
Diabetes mellitus	14 (45.2)	
Systolic blood pressure, mmHg	151 $\pm$ 25	120 – 220
Diastolic blood pressure, mmHg	90 $\pm$ 11	70 – 114
Total cholesterol, mg/dl ^a	183 $\pm$ 50	73 – 293
LDL cholesterol, mg/dl ^a	117 $\pm$ 37	67 – 202
HDL cholesterol, mg/dl ^a	43 $\pm$ 9	28 – 68
Triglycerides, mg/dl ^b	212 $\pm$ 121	50 – 542
Antihypertensive use	25 (80.6)	
Statin use	19 (61.3)	
History of CHD	12 (38.7)	
Family history of CVD	10 (32.3)	

^aTo convert to the international system of units (SI) (mmol/L), multiply by 0.0259;^bTo convert to SI units (mmol/L), multiply by 0.0113.

CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high density lipoprotein; LDL, low density lipoprotein; TIA, transient ischemic attack.

Table 2

Comparing IPH+ plaques between the symptomatic and asymptomatic side.

	Carotid plaques with IPH		p-value for difference	Correlation ^d	
	Symptomatic side	Asymptomatic side		Spearman's rho or odds ratio	p-value for correlation
Plaque location ^b			>0.99	11.5	0.038 ^d
Below flow divider, n (%)	5 (16.1)	6 (19.4)			
At/above flow divider, n (%)	26 (83.9)	25 (80.6)			
Percent luminal stenosis, %	53 ± 42	53 ± 39	0.99	0.51	0.006 ^d
IPH signal characteristics					
T1 signal (SIR _{IPH-to-muscle})	5.8 ± 2.4	4.7 ± 1.8	0.004 ^d	0.57	0.001 ^d
T2 signal			>0.99	1.33	0.84
Hypointense	15 (48.4)	17 (54.8)			
Hyperintense	4 (12.9)	6 (19.4)			
Mixed ^c	12 (38.7)	8 (25.8)			
IPH length, mm	14 ± 7	12 ± 8	0.12	0.44	0.012 ^d
Maximum IPH area, mm ²	17 ± 17	13 ± 10	0.21	0.44	0.014 ^d
IPH volume, mm ³	150 ± 199	88 ± 106	0.071	0.46	0.010 ^d
Plaque morphology					
Maximum wall thickness, mm	5.3 ± 1.6	4.7 ± 1.7	0.11	0.16	0.38
Plaque length, mm	24 ± 6	21 ± 7	0.026 ^d	0.28	0.13
Mean wall thickness, mm	2.1 ± 0.5	2.0 ± 0.5	0.43	0.00	0.99
Maximum percent wall area, %	77 ± 12	73 ± 11	0.071	0.16	0.37
Percent wall volume, %	60 ± 8	59 ± 9	0.62	0.14	0.45
Coexisting plaque characteristics					
LRNC volume, mm ³	406 ± 354	291 ± 293	0.039 ^d	0.16	0.38
Calcification volume, mm ³	54 ± 51	55 ± 95	0.90	0.16	0.38
Thin/ruptured fibrous cap, n (%)	24 (77.4)	21 (67.7)	0.55	1.82	0.65
Surface ulceration, n (%)	13 (41.9)	10 (32.3)	0.55	3.00	0.25
Mural thrombus, n (%)	9 (29.0)	3 (9.7)	0.11	1.25	>0.99

^aCorrelations between symptomatic and asymptomatic sides were assessed using Spearman's rank correlation coefficient (rho) for continuous variables and odds ratio for binary variables.

^bPlaque location was determined on carotid MRI by comparing the slice with largest plaque burden (maximum percent wall area) relative to the flow divider;

^cNot included in statistical analyses;

^d $p<0.05$.

IPH, intraplaque hemorrhage; LRNC, lipid-rich necrotic core; SIRIPH-to-muscle, signal-intensity-ratio as compared to muscle.