ORIGINAL RESEARCH

Vessel wall MRI characteristics associated with intra-procedural stent thrombosis during angioplasty for intracranial atherosclerotic stenosis

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ABSTRACT

Background Few studies have so far explored plaque characteristics on high-resolution magnetic resonance vessel wall imaging (HR-VWI) associated with intra-procedural stent thrombosis (IPST) during angioplasty for intracranial atherosclerotic stenosis (ICAS). We aimed to investigate the plaque features on HR-VWI associated with IPST during stenting for ICAS.

Methods This study recruited 77 patients with ICAS who underwent intracranial stenting using the Gateway-Wingspan system, and were performed with enhanced pre- and post-contrast T1-weighted HR-VWI on a 3.0T MRI scanner before angioplasty. During stenting for ICAS, eight patients (male: 100%, age mean ± standard deviation (SD): 58.7±2.47) developed IPST within 30 minutes after stenting. To ensure comparability, 16 patients who had undergone intracranial stenting but did not develop IPST were matched as controls for this study. Univariable and binary logistic models were used to explore the plaque characteristics on HR-VWI associated with IPST.

Results Patients who developed IPST had less plaque diffusion (37.50% vs 81.25%, p<0.036), a more severe degree of area stenosis (median 96.30% vs 81.65%, p<0.01), and a higher plaque enhancement index (median 37.99 vs 13.12, p=0.036) compared with those who did not. After multivariate adjustment, IPST was independently associated with a more severe degree of area stenosis (adjusted odds ratio (OR) 1.20, 95% confidence interval (CI) 1.01–1.43, p=0.044) and a higher plaque enhancement index (adjusted OR 1.17, 95% CI 1.01 to 1.36, p=0.036).

Conclusion Intra-procedural stent thrombosis during intracranial angioplasty for patients with ICAS may be independently associated with a higher plaque enhancement index and a more severe degree of area stenosis on HR-VWI.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Intra-procedural stent thrombosis (IPST) was an important complication during angioplasty for symptomatic intracranial atherosclerotic stenosis (ICAS). Previous studies have revealed several clinical risk factors associated with IPST, including antiplatelet resistance, long stenotic lesions, and use of multiple stents. High-resolution magnetic resonance vessel wall imaging (HR-VWI) can visualize the structure of the intracranial arterial wall and reveal the characteristics of high-risk plaques associated with ischemic stroke.

WHAT THIS STUDY ADDS

⇒ This study found that a higher plaque enhancement index and a more severe degree of area stenosis on HR-VWI might be associated with IPST in patients who underwent intracranial stenting.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests the association between plaque characteristics on HR-VWI and IPST may be potentially helpful in angioplasty risk assessment and preoperative preparation for intracranial stenting.

INTRODUCTION

Stroke is the second leading cause of death globally and the primary cause of death in China.1,2 Intracranial atherosclerotic stenosis (ICAS) is one of the leading causes of ischemic stroke in Asians, accounting for 46.6% of all ischemic stroke,3 while it only accounts for 10–15% of ischemic stroke in Western countries.4 Although most studies have shown that stenting and medical therapy have a similar effect and safety on patients with ICAS,5 individual studies have found that stenting compared with medical therapy resulted in an increased risk of stroke or transient ischemic attack (TIA).6 Among those studies, intra-procedural stent thrombosis (IPST) is a major risk factor for stroke recurrence and occurs in approximately 10.4% to 16.3% of patients who underwent stent placement.7 IPST, defined as a new, reappearing, or increasing thrombus, either occlusive or nonocclusive, within or adjacent to a stent implanted during the procedure, was first reported as a relatively rare but potentially serious event during percutaneous coronary intervention with drug-eluting stents.8 IPST was also an important complication during angioplasty for symptomatic ICAS. Previous studies found several clinical risk factors associated with IPST during carotid artery stenting, including antiplatelet resistance, long stenotic lesions, and use of more than one stent.9 Some studies on cardiovascular disease have shown that multiple plaque ruptures with large cavities more often evolve into IPST if...
they used intravascular ultrasound (IVUS), which can visualize the structure of plaques. IVUS may not be suitable for curved intracranial arteries to evaluate the nature of plaques. High-resolution magnetic resonance vessel wall imaging (HR-VWI) can visualize the lumen and reveal high-risk plaque characteristics associated with ischemic stroke, such as plaque eccentricity, intra-plaque hemorrhage, and wall enhancement. Therefore, the plaque characteristics of symptomatic ICAS are usually evaluated via non-invasive HR-VWI. However, to the best of our knowledge, no previous study has characterized the plaque features on HR-VWI associated with IPST.

Therefore, the purpose of our study was to investigate the association between the plaque characteristics on HR-VWI and the occurrence of IPST in patients treated with intracranial stenting.

**MATERIALS AND METHODS**

**Study population**

This study used data from a prospectively maintained database of 145 patients who received intracranial angioplasty at Shandong Provincial Hospital Affiliated to Shandong First Medical University. Patients were recruited from December 2016 to June 2022. The selection criteria for intracranial angioplasty therapy were as follows. Inclusion criteria: (1) Digital subtraction angiography (DSA) showed severe ICAS (≥70%); (2) Suffered from recurrent ischemic events (TIA or ischemic stroke defined by WHO criteria) after intensive drug therapy; (3) Inadequate tissue perfusion downstream of the targeted arterial segment; (4) Having at least one risk factor for atherosclerosis; (5) At least 3 weeks after the latest ischemic event. Exclusion criteria: (1) Clinical evidence of the presence of inflammatory arteritis, Moyamoya disease, intracranial tumors, aneurysms, or arteriovenous malformations; (2) Patients who had suffered from a large cerebral infarction (≥1/2 territory of middle cerebral artery or vertebrobasilar artery; (3) Patients with lesion length greater than 14 mm. This study used HR-VWI to evaluate the plaque characteristics of ICAS, including pre-enhanced and post-enhanced T1WI sequences. Inclusion criteria included: (1) Undergoing HR-VWI within 7 days before stenting; (2) Using the Gateway-Wingspan system (Stryker, US). The exclusion criteria included: (1) Insufficient image quality; (2) More than one stent implanted. Finally, 77 patients were included in the analysis. Figure 1 shows a flowchart of this study.

Baseline clinical and imaging data from the database was analyzed for all eligible patients. Thromboelastogram testing was performed for all patients after they had undergone dual antiplatelet therapy for at least 5 days. Once antiplatelet resistance was detected, the patient was treated with cilostazol instead. Demographic and clinical data were collected.

**Figure 1** Flowchart of patients in this study.

**Key:** HR-MRI, high-resolution MRI; IPST, intraprocedural stent thrombosis.
including age, sex, hypertension, diabetes mellitus, hyperlipidemia, smoking, alcohol consumption, and location of stent placement.

This study protocol was approved by the Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University (SWYX: NO.2021-012), and written informed consent was obtained from all participants.

High-resolution magnetic resonance vessel wall image acquisition
The detailed methods of acquiring vessel wall images are in the online supplemental materials.

Image processing and analysis
The part methods of image processing and analysis are in the online supplemental materials. The degree of area stenosis was calculated as (area of one lumen of the stenotic lesion/area of the reference lumen) × 100%.\(^\text{14}\) Irregularity in the plaque surface was defined as discontinuity in the juxtaposed surfaces of the plaque, whereas regularity was defined as a smooth inner wall. Plaques spreading across four quadrants were defined as diffusion, and that involving ≤3 quadrants were defined as non-diffusion.\(^\text{15}\) Plaque eccentricity was defined as a localized plaque encircling less than 75% of the vessel wall or the thickest portion being greater than twice the thinnest portion.\(^\text{16}\) Intraplaque hemorrhage (IPH) was defined as signal intensity greater than 150% of the adjacent muscle T1 signal. The remodeling index (RI) was the ratio of the vessel at the stenotic lesion to the area of the reference vessel. The vessel wall area index was the ratio of the vessel wall area at the stenotic lesion to the reference vessel wall area.\(^\text{14}\) The remodeling categories were based on reference intake (RI) values; RI ≥1.05 was considered positive remodeling (PR), RI ≤0.95 was considered negative remodeling (NR), and 0.95 <RI < 1.05 was considered no remodeling.\(^\text{15}\) Plaque enhancement was quantified by manually tracing the lumen and outer edge vessel wall at the narrowest part of the responsible vessel and measuring the signal intensity of the plaque (SI plaque) on matched pre-contrast and matched post-contrast 3D T1 images. A 10–12 mm\(^2\) circular area was plotted on the contralateral or proximal normal vessel wall on the matched pre-contrast and post-contrast T1-weighted images, respectively, and the signal intensity of the normal vessel wall was measured (SI normal vessel wall). The SI normal vessel wall located contralateral or proximal to the stenotic segment was evaluated as the reference. The enhancement grade was divided into three levels: no enhancement plaque group (grade 1, NO group, indicating enhancement was similar to or less than that of intracranial arterial walls without plaque in the same individual, mild enhancement group (grade 2, ME group, showing enhancement was greater than that of the NO group but less than that of the pituitary stalk), and significant enhancement group (grade 3, MA group, indicating similar or greater enhancement than the pituitary stalk).\(^\text{17}\) The enhancement index was calculated as follows: ((SI plaque/SI normal wall on post-contrast imaging) - (SI plaque/SI normal wall on matched pre-contrast imaging)) / (SI plaque/SI normal wall on matched pre-contrast imaging).\(^\text{18}\) All disagreements were resolved by consensus.

The intra-observer reliability of measuring and assessing the vessel wall was determined by the intra-group correlation coefficient (ICC) and Cohen’s kappa value. A value of ICC and kappa >0.75 indicates excellent agreement.

Perioperative management and stenting procedures
The detailed methods used in stenting are in the online supplemental materials.

Statistical analysis
All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). The detailed methods are in the online supplemental materials.

RESULTS
Clinical characteristics of study participants
All patients in the IPST group were male. Consequently, 16 male patients without IPST were matched for analysis. All patients underwent HR-VWI 2.8±1.5 days before intracranial stenting. There were no significant differences between the IPST group and the non-IPST group in age, sex, smoking, alcohol consumption, hyperlipidemia, hypertension, diabetes, diameter stenosis degree and time interval between HR-VWI and intracranial stenting (online supplemental table 1). Seven out of 8 patients in the IPST group were in good postoperative condition, with no complications such as infarction or bleeding. One patient suffered from postoperative symptoms of lung infection and dyspnea, but was soon discharged with symptomatic improvement.

Intraclass correlation coefficients to assess agreement of vessel wall measurements
The intraclass correlation coefficient (ICC) values were 0.95 (95% CI 0.86 to 0.98) for area stenosis degree, 0.96 (95% CI 0.90 to 0.98) for wall area index, 0.95 (95% CI 0.88 to 0.98) for enhancement index, and 0.93 (95% CI 0.87 to 0.97) for remodeling index. The Kappa values were 0.82 for plaque irregularity, 0.91 for plaque eccentricity, 0.91 for plaque diffusion, and 1.00 for intraplaque hemorrhage.

Quantitative analysis of plaques
As shown in table 1, patients with IPST showed less plaque diffusion (37.50% vs 81.25%, p=0.036), higher plaque enhancement index (median 37.99 vs 13.12, p<0.01), and more severe degree of area stenosis (median 96.30% vs 81.65%, p<0.01) compared with those without IPST. Figure 2 exhibited an example of one patient with IPST.

Association between IPST and plaque characteristics on HR-VWI
After adjusting for age, less plaque diffusion (Model 1: age-adjusted OR (OR) 0.09; 95% CI (CI), 0.01–0.87), higher plaque enhancement index (Model 1: age-adjusted OR, 1.10; 95% CI, 1.02 to 1.19), and more severe degree of area stenosis (Model 1: age-adjusted OR, 1.19; 95% CI, 1.02 to 1.39) remained significantly associated with IPST (table 2).

Model 2 was adjusted for variables with p<0.1 in the univariate analysis, which included age, hypertension, diabetes, smoking, alcohol consumption, and regularity in the plaque surface. After adjusting for multiple confounders, higher plaque enhancement index (Model 2: adjusted OR, 1.17, 95% CI 1.01 to 1.36, p=0.036) and more severe degree of area stenosis (Model 2: adjusted OR, 1.20, 95% CI 1.01 to 1.43, p=0.044) on HR-VWI was independently associated with IPST that occurred during intracranial stenting. However, the association between IPST and plaques diffusion was diluted and became statistically non-significant after adjusting for multiple confounders (Model 2: adjusted OR, 0.02; 95% CI, 0.00 to 1.36).
Neuroimaging

Table 1  Comparison of plaque characteristics between IPST and non-IPST groups

<table>
<thead>
<tr>
<th>Characteristics of plagues</th>
<th>IPST group (n=8)</th>
<th>Non-IPST group (n=16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque regularity, n (%)</td>
<td>7 (87.50)</td>
<td>8 (50.00)</td>
<td>0.080</td>
</tr>
<tr>
<td>Plaque eccentricity, n (%)</td>
<td>2 (25.00)</td>
<td>1 (6.25)</td>
<td>0.200</td>
</tr>
<tr>
<td>Plaque diffusion, n (%)</td>
<td>3 (37.50)</td>
<td>13 (81.25)</td>
<td>0.036</td>
</tr>
<tr>
<td>Area stenosis degree</td>
<td>96.30 (89.3, 99.0)</td>
<td>81.65 (75.0, 89.4)</td>
<td>0.009</td>
</tr>
<tr>
<td>Remodeling index</td>
<td>0.94 (0.31)</td>
<td>0.90 (0.34)</td>
<td>0.745</td>
</tr>
<tr>
<td>Remodeling categories, n (%)</td>
<td>2 (25.00)</td>
<td>3 (29.00)</td>
<td>0.519</td>
</tr>
<tr>
<td>Positive remodeling</td>
<td>2 (25.00)</td>
<td>5 (31.25)</td>
<td></td>
</tr>
<tr>
<td>Negative remodeling</td>
<td>3 (37.50)</td>
<td>10 (62.50)</td>
<td></td>
</tr>
<tr>
<td>No remodeling</td>
<td>3 (37.50)</td>
<td>1 (6.25)</td>
<td></td>
</tr>
<tr>
<td>Wall area index</td>
<td>1.21 (0.46)</td>
<td>1.43 (0.80)</td>
<td>0.499</td>
</tr>
<tr>
<td>Enhancement grade, n (%)</td>
<td>0.5 (0.46)</td>
<td>1.2 (0.96)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>0 (0.00)</td>
<td>2 (12.50)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>7 (87.50)</td>
<td>12 (75.00)</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>8 (100.00)</td>
<td>2 (12.50)</td>
<td></td>
</tr>
<tr>
<td>Enhancement index</td>
<td>37.99 (21.2, 46.9)</td>
<td>13.12 (12.1, 25.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>IPH, n (%)</td>
<td>1 (12.50)</td>
<td>2 (12.50)</td>
<td>0.999</td>
</tr>
</tbody>
</table>

Continuous variables were represented as median (IQR) and mean (SD). Categorical variables were represented as frequency and percentage.

IPH, intraplaque hemorrhage; IPST, intraprocedural stent thrombosis.

Figure 2  DSA of one patient with IPST. One adult patient presented with right limb weakness for 1 month. (A) Acute infarction in the center of the left semioval. (B) A diffuse distributive plaque in HR-VWI. (C) T1-weighted image after gadolinium injection. (D) Severe left internal carotid artery stenosis. (E) DSA showed stent thrombosis at 5 minutes after stent placement. (F) Complete recanalization after treatment with tirofiban.

Key: DSA: digital subtraction angiography; IPST, intraprocedural stent thrombosis; HR-VWI: high-resolution magnetic resonance vessel wall imaging.

DISCUSSION

In this study, we found that a higher plaque enhancement index and more severe degree of area stenosis may be independently associated with IPST in patients who underwent intracranial stenting. Our finding may be helpful in angioplasty risk assessment and preoperative preparation for intracranial stenting. Previous studies found that antiplatelet resistance, long stenotic lesions, and use of more than one stent were associated with IPST. In this study, patients were treated with cilostazol when antiplatelet resistance was detected. Moreover, all patients were treated with only one Wingspan stent and followed a consistent procedure and standardized perioperative management, thus minimum potential interference to the largest extent. To our knowledge, this is the first study to investigate intracranial plaque characteristics associated with IPST during angioplasty for patients with ICAS.

Table 2  Association of plaque characteristics on HR-VWI with IPST

<table>
<thead>
<tr>
<th>Characteristics of plagues</th>
<th>Model 1*</th>
<th>Model 2*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% confidence interval)</td>
<td>P value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Plaque diffusion</td>
<td>0.09 (0.01, 0.87)</td>
<td>0.038</td>
</tr>
<tr>
<td>Area stenosis degree</td>
<td>1.19 (1.02, 1.39)</td>
<td>0.026</td>
</tr>
<tr>
<td>Enhancement index</td>
<td>1.10 (1.02, 1.19)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

*OR and 95%CI were estimated from the multiple logistic regression models. Model 1 was adjusted for age. Model 2 was adjusted for age, hypertension, diabetes, smoking, alcohol consumption and regularities in the plaque surface.

CI, confidence interval; HR-VWI, high-resolution magnetic resonance vessel wall imaging; IPST, intraprocedural stent thrombosis; OR, odds ratio.

Some studies on coronary and carotid artery atherosclerosis have shown that plaque enhancement is related to plaque vulnerability. Previous studies on HR-VWI about the pathological
specimen from carotid endarterectomy have shown that enhanced plaque was associated with abundant active inflammatory cells, neo-vessel formation, and fibrous cap thinning. The exact mechanism of intracranial plaque enhancement remains unclear because specimens are relatively inaccessible. However, we can understand the pathophysiology of plaque enhancement in the vessel wall of cerebral arteries through previous studies on extracranial carotid arteries. Previous studies also suggested that intracranial plaque enhancement on HR-VWI was associated with neovascularization, inflammation, and endothelial dysfunction leading to gadolinium leakage. Therefore, higher plaque enhancement, more active inflammation persisted in the plaque after stent placement promoted subsequent thrombosis. In the aforementioned studies, carotid plaque gadolinium enhancement has been associated with histological markers of vessel wall neovascularization and inflammation, both well-known markers of unstable atherosclerotic plaque. Enhancement detectable on MRI may be related to endothelial dysfunction present in the diseased intraplaque microvasculature of atherosclerotic vessels. Such compromised microvascular endothelium may result in vascular leakage needed for gadolinium to accumulate in the perivascular spaces and become detectable on T1-weighted MRI sequences. An analogous process may occur in the intracranial vasculature. Thus, instability of atherosclerotic plaques secondary to neointima formation and inflammation can manifest itself as an acute thrombotic event. When the fibrous cap of vulnerable plaque ruptures under the influence of stenting, the plaque contents and the attached thrombus fall into the area covered by the stent and lead to thrombosis.

The degree of area stenosis is believed to be associated with ischemic stroke. Numerous studies have shown a significant association between vascular stenosis and the development and recurrence of symptomatic plaques or ischemic stroke. In this study, we found a more severe degree of area stenosis in the IPST group compared with the non-IPST group. One possible mechanism is that severe ipsilateral stenosis is related to longer reperfusion times. Another possible mechanism is that severe stenosis may place hemodynamic stress on brain circulation, which could lead to local endothelial injury, thrombus formation, plaque remodeling and rupture.

Vessels for intracranial stenting treatment including middle cerebral artery (MCA), basilar artery (BA), intracranial segment of internal carotid artery (ICA), and intracranial segment of vertebral artery (VA) were all involved in this study. There may be some differences in the structure of intracranial arteries in different segments especially for the intracranial segment of ICA considering the existence of vasa vasorum. Considering its potential effect, we analyzed the plaque characteristics of patients who underwent ICA stenting, although the sample was too small. We found that the enhancement index in the IPST group was higher than that in the non-IPST group, whether the patient underwent ICA stenting or other intracranial artery (MCA, BA and VA) stenting. Therefore, the effect of vasa vasorum in cavernous ICA on the results may be negligible in this study.

Our study had several limitations. First, the study included only eight patients with IPST, which may result in limited statistical power. In addition, all patients in the IPST group were male, potentially limiting the generalizability to female patients. Therefore, further studies are warranted in the future. Thirdly, all patients used the Gateway-Wingspan system, so the findings may be more applicable to patients proposed for self-expanding stents. Finally, this was a retrospective analysis, and only patients who underwent HR-VWI were included, which might introduce a bias in patient selection. The findings of this study should be further validated in larger-scale prospective multicenter studies.

CONCLUSION Intraprocedural stent thrombosis during angioplasty for patients with ICAS may be independently associated with a higher plaque enhancement index and a more severe degree of area stenosis on HR-VWI.

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