Remodeling of occluded internal carotid artery in vessel wall magnetic resonance imaging

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ABSTRACT

Objective: The purpose of the present study was to investigate the remodeling pattern of the extracranial occluded internal carotid artery (OICA) by vessel wall magnetic resonance imaging (VWI).

Methods: Thirty-nine atherosclerotic OICAs from 32 consecutive cases underwent 3-Tesla VWI to acquire pre- and post-contrast T1-weighted two-dimensional fluid-attenuated inversion recovery fast spin echo sequences. 25 symptomatic CAs exhibited ipsilateral downstream cerebral ischemia or ophthalmic artery embolism within last three months. The 14 remaining CAs were asymptomatic. Twenty-four CAs from 22 patients with atherosclerosis but no stenosis were recruited as control group. The outer wall area (OWA) was calculated based on the outer contour of the carotid artery drawn on the pre-contrast VWI. Negative remodeling was defined as a lower OWA compared to that of control group.

Results: Clinical characteristics including age, sex and vascular risk factors showed no significant difference between the occluded and control group. However, the OWA was lower in the occluded group than in the control group (0.63 versus 0.90 cm², \(p=0.004\)). For all OICAs, the OWA was larger in symptomatic cases than asymptomatic cases (0.71 versus 0.49 cm², \(p=0.025\)). Using a cutoff value of 0.44, the sensitivity and specificity of OWA for detecting symptomatic OICA were 0.88 and 0.57, respectively. Heterogeneous signal intensity and enhancement were more often observed at the proximal than the distal segment of occlusion (\(p<0.001\)). The inter-observer agreement regarding the evaluation of VWI characteristics was desirable (\(k=0.805\)).

Conclusions: Negative remodeling is prevalent in OICA, especially in asymptomatic cases.

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Introduction

Patients with occluded internal carotid artery (OICA) may very likely develop undesired short- or long-term consequences [1–3]. In the clinic, neurological manifestations of acute occlusion range from being completely asymptomatic to severe ipsilateral downstream ischemic stroke [4]. Furthermore, chronic occlusion tends to cause a progressive process due to insufficient cerebral perfusion and microembolization [5,6]. Endovascular treatment is currently the standard approach for improving the therapeutic outcome of acute OICA and has also been used for the recanalization of chronic occlusion [7,8] although with a relatively low success rate and severe complications [9]. Therefore, the assessment of the occlusion phase is critical to determine the optimal management regimen for preventing stroke.

Previous studies have proposed the ‘ring sign’ in CT angiography (CTA) as a differentiating feature between acute and chronic occlusion [10]; however, the conclusion needs further validation. High-resolution contrast-enhanced vessel wall magnetic resonance imaging (VWI) enables direct visualization of wall thickening [11–13] and atherosclerosis plaque composition [12,14]. Preliminary reports have demonstrated the feasibility of VWI for the assessment of large vessel occlusion [15,16]; however, the suitability of this approach for identifying occlusive vasculopathies,
especially acute and chronic occlusions, remains subject to debate.

It is well known that arteries experience positive, negative or intermediate remodeling throughout the development of atherosclerosis [17–19]. So far, the carotid artery (CA) remodeling during OICA is unclear, although the expansion of the artery or the positive remodeling observed in CA with stenosis always indicates the presence of ischemic symptoms [20,21]. For all these reasons, the aim of this prospective pilot study was to explore the remodeling pattern of CA with occlusion using VWI and in turn, assess its contribution to the differentiation between acute and chronic occlusion.

Materials and methods

Patients

Thirty-eight patients were prospectively and consecutively enrolled between November 2014 and March 2019. In total, 46 atherosclerotic OICAs were detected by ultrasound or magnetic resonance angiography (MRA). Inclusion criteria included the following: (1) extracranial OICA showed by ultrasound or MRA; (2) two or more (>50 years old for men or >60 years old for women, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease and current cigarette smoking). Exclusion criteria involved the detection of moyamoya disease, arteritis, dissection or embolic occlusion. All participants underwent a routine brain MRI (magnetic resonance imaging) to verify a new ischemic attack – arteritis, dissection or embolic occlusion. All patients provided written informed consent. All participants underwent a brain MRI (magnetic resonance imaging) to verify a new ischemic attack that could not tolerate the MR examination because of medical instability or claustrophobia. Insufficient image quality led to the exclusion of another three patients. Then totally, 32 patients with 39 OICAs were included in this study. Symptomatic OICA was defined as occlusion accompanied by ipsilateral downstream acute ischemic symptoms, such as transient ischemic attack, infarction in the anterior circulation territory or ophthalmic artery embolism within the most recent three months. Otherwise, the case was defined as asymptomatic OICA. Moreover, 24 CAs from 22 patients with more than two atherosclerotic risk factors but no stenosis were selected as the atherosclerotic controls (control group). This study was approved by the local medical ethics committee and all patients provided written informed consent.

MR imaging protocol

A 3.0 Tesla MR scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany) with a 16- or 64-channel head coil and a four-channel phased-array carotid coil was used to perform a multi-sequence contrast-enhanced MR protocol without electrocardiographic gating or motion correction. This protocol included the following steps: (1) three-dimensional time-of-flight (TOF) angiography for image positioning (slice thickness of 1 mm; repetition time (TR)/echo time (TE) of 20/3.27 ms; flip angle of 25°; field of view (FOV) of 230 × 195 mm; matrix of 384 × 245; number of slices: 40; and a total time of 2:58 min); (2) a fat- and blood-suppressed 2D T1 Turbo Spin Echo (TSE) sequence (slice thickness of 2 mm; TR/TE of 1000/26 ms; flip angle of 120°; FOV of 140 × 140 mm; averages of 3; matrix of 256 × 256; number of slices: 14; and a total time of 4:34 min) before (T1) and after (post-contrast T1) intravenous administration of gadopentetate dimeglumine (Beilu Pharmaceutical Co., Ltd., Beijing, China) at a dose of 0.2 mmol/kg and an injection rate of 3–4 ml/s; 3) a fat- and blood-suppressed 2D T2 TSE sequence (slice thickness of 2 mm; TR/TE of 2500/60 ms; flip angle of 120°; FOV of 140 × 140 mm; averages of 3; matrix of 256 × 256; number of slices: 14; and a total time of 2:55 min). The images were centered at the level of the carotid bifurcation with a total scan time of approximately 15 min.

Image analysis

Five consecutive slices of extracranial internal carotid artery (ICA) from first image showing occlusion (i.e. O1, O2, O3, O4 and O5) were independently analyzed by two experienced neuroradiologists who were blinded to the clinical data. Discrepancies were resolved by consensus. First, by comparison with the adjacent sternocleidomastoid muscle, the intraluminal signal intensity (SI) was measured on the T1 image and categorized as hypo-, iso- or hyperintensity. The uniform shape of the SI was considered homogeneous while a mixed shape was considered heterogeneous. Second, the presence and pattern of enhancement were determined by comparing pre- and post-contrast T1 images, with >50% of area defined as major enhancement, 20–50% as minor enhancement and <20% or at lesion sites as focal enhancement. Third, as the luminal diameters of the CA were immeasurable after occlusion, the outer wall area (OWA) was measured to denote the remodeling pattern, which was calculated from the semi-automatically drawn contours on the T1 image by the Vesselmass software (Leiden
University Medical Center, the Netherlands). Negative remodeling was defined as an OWA being less than that of the control group. Fourth, the carotid ring sign, indicating the presence of hypointensity in the lumen of the occluded CA or the ring-like contrast enhancement in the carotid wall, was identified on the post-contrast T1 image [10].

Statistical analysis

All data were analyzed using the SPSS software for Windows version 22 (SPSS Inc., USA). Continuous variables are expressed as the mean ± SD and compared using an independent t-test. The categorical variables are presented as numbers (percentage) and compared using a chi-square or Fisher’s exact test. Receiver operating characteristic curve (ROC) analysis was conducted to assess the strength of OWA in predicting the presence of acute symptoms. For all analyses, \( p < 0.05 \) was considered statistically significant. Inter-observer agreement was analyzed using Cohen’s \( \kappa \) coefficient, with \( \kappa \leq 0 \) indicating poor agreement, \( \kappa = 0–0.20 \) slight agreement, \( \kappa = 0.20–0.40 \) fair agreement, \( \kappa = 0.40–0.60 \) moderate agreement, \( \kappa = 0.60–0.80 \) substantial agreement and \( \kappa = 0.80–1.0 \) excellent agreement.

Results

In total, 32 patients (24 males; mean age: 56.1 ± 9.6 years; range: 37–80 years) with 39 OICAs (7 patients had bilateral occlusion) were included in the current study. For the 25 symptomatic OICAs, the mean National Institutes of Health Stroke Scale (NIHSS) score was 2.7 ± 4.5 (range: 0–22), and the mean interval between symptom onset and VWI examination was 22 ± 16 days (range: 4–70 days). Fourteen asymptomatic OICAs were identified in routine examinations. Of all 39 OICAs, 14 exhibited total luminal occlusion at the level of the carotid bifurcation and 25 had remaining stumps (Supplementary Table S1).

Age, sex, risk factors for ischemic stroke (hypertension, hyperlipidemia, diabetes mellitus, ischemic heart disease and smoking habit) and history of stroke were not significantly different between the OICA and atherosclerotic control groups (\( p > 0.05 \), Supplementary Table S2). The OWA was smaller in OICAs compared to controls across all segments (e.g. O1 segment, 0.63 ± 0.31 cm\(^2\) vs. 0.90 ± 0.39 cm\(^2\), \( p = 0.004 \), Table 1). For OICA group, the OWA was greater in symptomatic than in asymptomatic patients (e.g. O1 segment, 0.71 ± 0.29 cm\(^2\) vs. 0.49 ± 0.30 cm\(^2\), \( p = 0.025 \), Table 1). The presence of the remaining stump did not affect the extent of OWA in the OICA group (e.g. O1 segment, 0.65 ± 0.29 cm\(^2\) vs. 0.60 ± 0.35 cm\(^2\), \( p = 0.590 \), Table 1). ROC analysis on the predictive value of OWA at the O1 segment for an acute ischemic event found that the area under the curve (AUC) was 0.746 (95% CI 0.577–0.915, \( p = 0.012 \)). When the cutoff value was set at 0.44, the sensitivity and specificity of using OWA to reveal symptomatic occlusion were 0.88 and 0.57, respectively (Table 2).

Thirty-seven out of the 39 images (94.9%) at the O1 segment showed a mixture of hyper-, iso- or hypointensity on the T1 image (Figure 1, left panel), while the remaining two images (5.1%) showed homogeneous hyperintensity. The images of occluded vessel residuals at the O1 segment after contrast all showed a heterogeneous pattern (Figure 1, middle left panel). Of which, 28 (71.8%) manifested as major enhancement (Figure 1(C)), 9 (23.1%) as minor enhancement (Figure 1(A)) and 2 (5.1%) as focal enhancement (Figure 1(B)). Neither the pattern of SI nor the enhancement showed a significant difference between symptomatic and asymptomatic occlusion groups and was also unaffected by the remaining stump (\( p > 0.05 \), Table 1).

As compared to the O1–O3 segments, more images at the O5 segment showed a homogeneous SI pattern (\( p < 0.001 \)) in both the symptomatic or asymptomatic groups. When the two cases with focal enhancement at the O5 segment (identified by two neuroradiologists as a large calcified plaque extending to the distal ICA) were excluded, more images at the O5 segment shows pattern of major enhancement than that at the O1 segment (\( p = 0.046 \)).

The carotid ring sign showed no difference between symptomatic and asymptomatic occlusion groups regardless of the presence of stumps (\( p > 0.05 \), Table 1). Of the 25 OICAs with remaining stumps, 17 (68%) showed no apparent plaque and only mild concentric wall thickening proximal to the occlusion segment (Figure 1(C), right panel).

For all the 195 images from 39 vessels, the interobserver agreement on the VWI findings (pattern of SI and enhancement) was deemed to be excellent (\( \kappa = 0.805–0.847 \), Supplementary Table S3).

Discussion

In this study, the OWA, SI pattern and enhancement of OICA were assessed using VWI. The results showed that patients with occluded extracranial ICA, especially
those without acute ipsilateral downstream ischemic symptoms, tended to exhibit negative remodeling of the vessel. This finding provides insight into the geometric changes of the arterial wall secondary to the occlusion and might be helpful for optimizing the revascularization procedure.

Considering the anatomical expanding of the carotid bulb and the possible expansive remodeling involved in the CA with atherosclerosis [20], we compared the OWA of OICA with that of ICA with atherosclerosis but no stenosis. The relationship between expansive remodeling in CA stenosis and downstream ischemic symptoms has been reported extensively [20–22]. However, in our study, except for two cases with huge calcific plaque, most OICA patients showed no significant expansion of the ICA (Figure 1), especially for the asymptomatic cases, which was also unaffected by the presence of a stump. The trend seems more significant at distal lesion from OICA as the AUC of OWA of O5 was the most significant in the five segments (Table 2). The mechanisms behind this finding could be the fact that some extracranial ICA occlusions are merely due to thrombosis or vessel collapse after distal artery embolism or plaque [23], but not the atherosclerotic plaque in situ. Similarly, in the current study, there was no obvious atherosclerotic plaque at the carotid stump in 68% of OICAs with a remaining stump. This finding coincides with previous reports indicating that the carotid occlusions were less likely to contain a large necrotic core compared to carotid stenosis [24]. Another reason for this may be that neovascularization through thrombus organization can occur along with the scarification of thrombus in chronic occlusion.

In the present study, all images of O1 segments showed a heterogeneous enhancement pattern on post-contrast T1 images while 94.9% images of O1 segments showed a mixture of hypo-, iso- or...
hyperintensity. These observations may relate to the presence of calcific, lipid or fibrotic plaques in situ [14]. Rupture of the thin fibrous cap exposes the thrombogenic lipid core to flowing blood, which promotes thrombosis formation and carotid occlusion [25]. Therefore, the basis of atherosclerotic occlusion involves an unstable plaque with lipids, intraplaque hemorrhage (IPH), fibrosis and calcification. Gadolinium agents have been found to preferentially enhance fibrous regions which can be applied to identify the lipid-rich necrotic core and calcification in non-enhancing regions [26,27]. However, IPH is hard
to predict in this way on VWI as the SI of the hemorrhage is dependent on the structure of hemoglobin and its oxidation state [28]. Besides, neovascularity [29], inflammation in the plaque [30] and vasa vasorum in the adventitial layer [31] may all contribute to wall enhancement. In the present study, the interval between symptom onset and VWI examination ranged from 4 to 70 days in the symptomatic group, which highlights the unpredictability of the enhancement pattern as some critical features would vary considerably over time. So future studies with patients getting VWI soon after the symptom onset will provide more accurate evaluation on the imaging characteristics of OICA. According to our study, the heterogeneous pattern of SI and enhancement in the distal segment of occlusion was not as prominent as that in the proximal segment. It has been known that most atherosclerotic plaques are centered at the carotid bifurcation (<10 mm from the bifurcation) [32]. So, the distal segment may be occupied by the thrombosis secondary to the occlusion instead of atherosclerotic plaque.

So far, 20%–40% of stroke patients present with extracranial ICA occlusion and the currently available interventional strategies are still insufficient [33–35]. Occlusion at a duration of >3 months is associated with lower recanalization rates and a higher complication incidence compared to that of <1 month (51% vs. 80% and 25% vs. 6%, respectively) [36]. However, there are still no reliable methods to classify the carotid occlusions as acute or chronic, delaying the screening of patients who might benefit from revascularization therapies. Hybrid surgery (i.e. endovascular techniques plus carotid endarterectomy) has been recommended in the recanalization of OICA with no remaining stump [37]. However, according to our study, for occlusion with a mild OWA, the endarterectomy should be carefully applied.

Previous studies have shown that the carotid ring sign in CTA may help discern acute from chronic occlusion [10]. However, in our study, the prevalence of a ring sign was similar between the symptomatic and asymptomatic groups, which may be associated with IPH, a frequent cause for acute vessel occlusion that shows as intraluminal hyperintensity on MRI [14]. On the other hand, the chronic occlusion secondary to large calcific plaques may display intraluminal hypointensity on MRI, resembling the ring sign on CTA (Figure 1(B)).

The present study has several limitations. First, we did not enroll unstable patients or those with large-sized infarctions, indicating that some cases with acute occlusion were underestimated and that the VWI information of symptomatic OICA may be biased. Second, there are no criteria to discriminate acute from chronic occlusions, and the subjects with acute ischemic symptoms were considered as having acute occlusion in the current work. However, the hemodynamic changes in chronic OICA could also induce an acute ischemic stroke, so some chronic cases may be included in the symptomatic OICA group. Third, the acute thrombosis, IPH or neovascularization was not validated by pathologic examinations in the present study. To address these limitations, a multi-center prospective study with the focus on the correspondence between VWI hallmarks and histological composition would be warranted.

In conclusion, we systemically investigated the remodeling, SI features and enhancement pattern in symptomatic and asymptomatic OICA. The current findings may facilitate the interpretation of occlusion and influence the selection of recanalization. Though further study is needed, the negative remodeling of OICA, especially in chronic cases is critical for devising a surgical intervention regimen.

Disclosure statement

The authors report no conflict of interest.

Ethical approval

The study was approved by the Medical Ethics Committee, Shandong Provincial Hospital, Cheeulo college of Medicine, Shandong University (No. 2018-212), Jinan, Shandong, 250021, China.

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