Differences in left and right carotid plaque vulnerability in patients with bilateral carotid plaques: a CARE-II study

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ABSTRACT

Background and purpose Atherosclerosis is a very complex process influenced by various systemic and local factors. Therefore, in patients with bilateral carotid plaques (BCPs), there may be differences in carotid plaque vulnerability between the sides. We aimed to investigate the differences in BCP characteristics in patients with BCPs using magnetic resonance vessel wall imaging (MR-VWI).

Methods Participants with BCPs were selected for subanalysis from a multicentre study of Chinese Atherosclerosis Risk Evaluation II. We measured carotid plaque burden, identified each plaque component and measured their volume or area bilaterally on MR-VWI. Paired comparisons of the burden and components of BCPs were performed.

Results In all, 540 patients with BCPs were eligible for analysis. Compared with the right carotid artery (CA), larger mean lumen area (p=0.001), larger mean wall area (p=0.029), larger mean total vessel area (p<0.001) and smaller normalised wall index (p=0.006) were found in the left CA. Regarding plaque components, only the prevalence of lipid-rich necrotic core (LRNC) in the left CA was higher (p=0.026). For patients with a vulnerable plaque component coexisting on both sides, only the intraplaque haemorrhage (IPH) volume (p=0.011) was significantly greater in the left CA than in the right CA.

Conclusions There were asymmetries in plaque growth and evolution between BCPs. The left carotid plaques were more likely to have larger plaque burden, higher prevalence of LRNC and greater IPH volume, which may contribute to the lateralisation of ischaemic stroke in the cerebral hemispheres.

BACKGROUND

Atherosclerosis occurring in extracranial carotid arteries (CAs) is one of the main causes of ischaemic stroke.1 Studies suggest that there is a strong association between vulnerable carotid plaques and ischaemic stroke.2–4 Several studies have found that ischaemic stroke preferentially occurs in the left cerebral hemisphere, in which carotid atherosclerotic disease was determined by B-mode ultrasound, CT and/or magnetic resonance (MR) angiography.5–8 Despite sharing common cardiovascular risk factors (CVRFs) and pathogenesis, atherosclerotic plaques vary in different parts of the vasculature.9 There may be a certain interplay between the CA anatomy, geometry and genesis of abnormal haemodynamic forces, which mainly serve as local factors of atherogenesis.10–12 However, evidence on this clinically concerned matter remains limited. Therefore, we hypothesised that local factors may cause differences in the evolution of bilateral carotid plaques (BCPs), as evidenced by BCPs with different plaque burden and plaque components in the same patient. Clarifying the differences in the vulnerability of BCPs may contribute to more accurate disease prevention and treatment.

The Chinese Atherosclerosis Risk Evaluation (CARE-II) study was designed to investigate the prevalence and characteristics of high-risk carotid atherosclerotic plaque in Chinese patients with ischaemic stroke and transient ischaemic attack using magnetic resonance vessel wall imaging (MR-VWI).13 MR-VWI is capable of accurately characterising
plaque morphology, components and surface condition, and has been extensively validated by histology.14 Moreover, a systematic review and meta-analysis summarised the key plaque features of MR-VWI, such as large lipid-rich necrotic core (LRNC), intraplaque haemorrhage (IPH) and fibrous cap rupture (FCR), which were significantly associated with ischaemic stroke.15 16 This study reanalysed the CARE-II data to evaluate the differences in plaque burden and components between BCPs in patients included.

METHODS
Study population
The participants were recruited from CARE-II, which was a cross-sectional, observational, multicentre study (http://www.clinicaltrials.gov; unique identifier: NCT02017756). The CARE-II study aimed to investigate the prevalence of high-risk carotid atherosclerotic plaques in patients with cerebrovascular symptoms. The design and rationale of the CARE-II study have been published.13 The original exclusion criteria comprised (1) cardiogenic stroke, (2) haemorrhagic stroke, (3) radiation therapy in the neck, (4) CA stenting or carotid endarterectomy, (5) claustrophobia and (6) contraindications to MRI. Figure 1 presents the flow chart of the patients. In the present study, we excluded patients with (1) missing clinical information (n=76), (2) poor image quality (n=98) and (3) unilateral extracranial carotid plaques (n=443). Clinical information was obtained from the medical records within 7 days before the MR-VWI examination for all patients. Demographics including age, sex, height and weight were recorded and the body mass index was calculated. Data on CVRFs including hypertension, smoking history, diabetes, hyperlipidaemia, and levels of total cholesterol, high-density and low-density lipoprotein, and triglycerides were collected. Hypertension was defined as diastolic blood pressure $\geq 90$ mm Hg or systolic blood pressure $\geq 140$ mm Hg and/or use of antihypertensive agents. Diabetes was defined as fasting serum glucose levels $\geq 7.0$ mmol/L and/or use of antidiabetic therapy. Hyperlipidaemia was defined as serum total cholesterol $\geq 5.17$ mmol/L and/or triglycerides $\geq 1.7$ mmol/L and/or high-density lipoprotein $\leq 1.04$ mmol/L and/or use of oral statins. Other clinical characteristics included a history of coronary heart disease and smoking habits. All study participants provided written informed consent.

MR-VWI protocol
Participating radiologists and MR technologists from each imaging site were trained regarding image acquisition and quality evaluation. The full imaging protocol and parameters for this study have been published.13 Briefly, MR-VWI was performed at each of the 13 participating centres using a 3.0T MR scanner (Achieva TX,
Philips Healthcare, Best, The Netherlands) with dedicated eight-channel phase array carotid coils. A standardised multicontrast imaging protocol was used to acquire the carotid images using the following parameters: three-dimensional (3D) time-of-flight (TOF)-fast field echo, repeat time (TR)/echo time (TE) 20/4.9 ms and flip angle 20°; T1-weighted imaging (T1WI) with quadruple inversion recovery-turbo spin echo, TR/TE 800/10 ms and flip angle 90°; T2-weighted imaging (T2WI) with multislice double inversion recovery-turbo spin echo, TR/TE 4800/50 ms and flip angle 90°; and magnetisation-prepared rapid gradient echo (MP-RAGE)-fast field echo, TR/TE 8.8/5.3 ms and flip angle 15°. All imaging sequences were acquired with the same field of view (140×140 mm²) and matrix (256×256). The slice thickness was 1 mm for 3D TOF and MP-RAGE and 2 mm for T1WI and T2WI, respectively. The main MR-VWI parameters are detailed in table 1.

### MR-VWI image interpretation

The multicontrast vessel wall images of bilateral CAs were interpreted by two trained reviewers (SS and HS, both with >3 years’ experience in cardiovascular plaque imaging) using custom-designed software (Cascade; University of Washington, Seattle, USA). Each axial image was reviewed by two reviewers blinded to the clinical information, and consensus was achieved with consultation. The lumen and wall boundaries were manually outlined to measure the lumen area, wall area, total vessel area and wall thickness at each axial location. The normalised wall index (wall area/total vessel area×100%) was calculated for each CA. 3D TOF MR angiography images were reconstructed by maximum intensity projection to measure the luminal stenosis of CAs using the North American Symptomatic Carotid Endarterectomy Trial algorithm. Severe stenosis was defined as luminal stenosis ≥50%. The variables mentioned above were used to assess plaque burden. The presence or absence of calcification, LRNC, IPH, FCR and high-risk plaque (HRP) was identified using published criteria. Briefly, IPH was defined as a hyperintense region within the plaque on TOF and T1WI, and particularly on MP-RAGE images. LRNC was determined when there was an isointense region on TOF and T1W images or a hypointense region on T2W images within the plaque. The disrupted luminal surface was identified when there was a deficit in the fibrous cap or discontinuous surface of the plaque. A large LRNC was defined as an LRNC that occupied more than 40% of the wall area on the axial image. Volumes were calculated from axial area measurements by summing and multiplying by the slice thickness. Per cent wall volume (%wall volume=100×wall volume/total vessel volume), component volumes and component % volumes (100×component volume/wall volume) were computed. The maximum percentage of the vessel wall occupied by each plaque component was calculated from the measured areas. The size of each plaque’s compositional feature was also measured with volumes or areas. HRP was defined as a lesion with IPH, FCR or maximum percentage LRNC area (max %LRNC) >40%. We have previously reported good to excellent intrareader and inter-reader reproducibility for wall thickness (intraclass correlation coefficient (ICC): 0.93–0.96), calcification area (ICC: 0.90–0.95), LRNC area (ICC: 0.89–0.92) and IPH area (ICC: 0.73–0.74).

### Statistical analysis

All statistical analyses were performed using SPSS for Windows V.23.0. Patients with BCPs identified by MR-VWI were selected to evaluate the differences in carotid plaque burden and compare each plaque component on one or both sides (1:1 pairwise matching for the left and right side for each patient). The clinical characteristics of the included patients were expressed as mean±SD or number (percentage). In patients with BCPs, carotid plaque burden and vulnerable plaque components were compared; paired t-test was used to compare paired medians and the McNemar test was used to compare the prevalence of each vulnerable plaque component bilaterally. Statistical test results were considered significant when p<0.05.

### RESULTS

Among the 1157 patients with acute ischaemic stroke/transient ischaemic attack registered in the CARE-II study, 540 were eligible for the present analysis. Information on patient demographics and the proportion of each CVRF is shown in table 2. Among the 540 symptomatic patients with BCPs, 331 had information regarding the symptomatic side, including 162 (48.9%) on the left side and 169 (51.1%) on the right side, with no significant difference in proportion between the two groups (p=0.700). The remaining 209 patients had no clear information on the symptomatic side (160 patients with unknown
symptomatic side and 31 patients with missing information on the symptomatic side).

Plaque burden in patients with BCPs
The mean lumen area (44.6±15.2 mm² vs 41.2±14.5 mm², p<0.001), mean wall area (35.3±12.1 mm² vs 34.3±11.9 mm², p=0.025) and mean total vessel area (80.0±21.2 mm² vs 75.5±20.7 mm², p<0.001) were significantly larger in the left CA than in the right CA. However, the normalised wall index (44.5%±9.4% vs 45.6%±9.6%, p=0.006) was significantly smaller in the left CA (table 3).

Vulnerable plaque components in patients with BCPs
The prevalence of various vulnerable plaque components in bilateral CAs was evaluated in patients with BCPs. LRNC (n=537, 99.4%) was the most common plaque component, followed by calcification (n=426, 78.9%), IPH (n=176, 32.6%) and FCR (n=86, 15.9%). The prevalence of HRP was 45.4% (n=245). When performing a left side–right side comparison, the prevalence of LRNC was slightly higher in the left CA than in the right CA (n=503 vs n=483, respectively; p=0.026). However, the prevalence of calcification, IPH, FCR and HRP was not significantly different (all p>0.05) (table 4). For patients with a specific vulnerable plaque component coexisting on both sides, the numbers of patients with IPH, LRNC, calcification, FCR and HRP were 47 (8.7%), 449 (83.1%), 265 (49.1%), 8 (1.5%) and 75 (13.9%), respectively (table 4 and figure 2). When comparing each vulnerable plaque component present in the BCPs of each patient, calcification volume (n=265; 25.3±48.5 mm³ vs 24.6±52.48 mm³, p=0.146), LRNC volume (n=449; 108.9±171.9 mm³ vs 114.1±183.9 mm³, p=0.337) and max %LRNC (n=449; 23%±18% vs 24%±19%, p=0.242) were not significantly different between the left and right CAs (all p>0.05). Only the IPH volume was significantly larger in the left CA (148.4±168.3 mm³ vs 87.5±106.0 mm³, p=0.011) in patients with IPH in BCPs (table 5). Figure 3 shows an example of HRPs with IPH coexisting bilaterally; the IPH volume was notably larger in the left CA than in the right CA.

DISCUSSION
In this study, we explored the differences in plaque burden and components between BCPs based on MR-VWI, which may contribute to clarifying the lateralisation of ischaemic stroke in the cerebral hemispheres. The results demonstrated that plaque burden was significantly higher in the left CA than in the right CA in patients with BCPs. The prevalence of LRNC was slightly higher in the left CA. Moreover, in patients with IPH coexisting in BCPs, the IPH volume was significantly larger in the left CA than in the right CA. This study indicates that in a single patient with common CVRFs, local factors may influence atherosclerosis, leading to asymmetrical plaque growth and evolution, suggesting that targeted treatments should be given when carotid plaques occur on the left and/or right side.

Important strengths of this study include its patient-based design and the inclusion of participants with BCPs.
only. Moreover, a standardised high-resolution, multi-contrast MR-VWI protocol for extracranial CAs was used, which could identify various carotid plaque components with good to excellent intrareader and inter-reader reproducibility. Finally, we paired and analysed plaque burden and components bilaterally in patients with BCPs in order to minimise selection bias due to CVRFs in different patients. Moreover, patients with a specific vulnerable plaque component coexisting in BCPs were selected for a quantitative comparison of each vulnerable plaque component between the sides. Exploring the differences in bilateral plaque burden and components may help elucidate the potential mechanisms of atherosclerotic plaque initiation and development, refine the stratification of stroke risk, and optimise individualised plans for clinical management.

In this study, 18.5% and 15.4% of the left and right CAs, respectively, had plaques with ≥50% lumen stenosis, showing a similar prevalence compared with previous reports of Chinese populations. In the Chinese Intracranial Atherosclerosis Study, severe atherosclerotic lesions (>50% stenosis) in extracranial CAs were found in 14% "P<0.05.

Table 4 Bilateral prevalence of vulnerable plaque features in symptomatic patients with BCPs (N=540)

<table>
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<tr>
<th>Presence of</th>
<th>n (%)</th>
<th>Present in at least one side</th>
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<tr>
<td></td>
<td>Neither bilaterally</td>
<td>Left side only</td>
</tr>
<tr>
<td>Presence of calcification</td>
<td>114 (21.1)</td>
<td>426 (78.9)</td>
</tr>
<tr>
<td>Presence of LRNC</td>
<td>3 (0.6)</td>
<td>537 (99.4)</td>
</tr>
<tr>
<td>Presence of IPH</td>
<td>364 (67.4)</td>
<td>176 (32.6)</td>
</tr>
<tr>
<td>Presence of FCR</td>
<td>454 (84.1)</td>
<td>86 (15.9)</td>
</tr>
<tr>
<td>Presence of HRP</td>
<td>295 (54.6)</td>
<td>245 (45.4)</td>
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*P<0.05.
†P value based on the comparison of various vulnerable plaque components between left and right carotid arteries (it counts when present in one side, regardless of whether it appears on the contralateral side).

**Figure 2** Bilateral presence of vulnerable plaque features in symptomatic patients with BCP. BCPs, concurrent bilateral carotid artery plaques; FCR, fibrous cap rupture; HRP, high-risk plaque; IPH, intraplaque haemorrhage; LRNC, lipid-rich necrotic core.
of patients with ischaemic stroke. In our previous study, 19% of participants had plaques with ≥50% carotid stenosis. A similar prevalence was found in Taiwanese (>50% stenosis: 13%) and Hong Kong (>50% stenosis: 18%) Chinese populations. A previous study reported that IPH and fibrous tissue were more prevalent in left CA plaques than in right CA plaques, while the lipid was distributed equally. Compared with their findings, our outcomes showed that LRNC was more prevalent in the left CA, while the prevalence of IPH was similar between

<table>
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<th>Table 5</th>
<th>Comparison of concurrent vulnerable plaque components bilaterally in symptomatic patients with BCPs</th>
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<tbody>
<tr>
<td>Mean±SD</td>
<td>Left carotid artery</td>
</tr>
<tr>
<td>Volume of calcification, mm³</td>
<td>25.3±48.5</td>
</tr>
<tr>
<td>Volume of LRNC, mm³</td>
<td>108.9±171.9</td>
</tr>
<tr>
<td>Volume of IPH, mm³</td>
<td>148.4±168.3</td>
</tr>
<tr>
<td>Max %LRNC, %</td>
<td>23±18</td>
</tr>
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</table>

*P<0.05.
BCPs, concurrent bilateral carotid plaques; IPH, intraplaque haemorrhage; LRNC, lipid-rich necrotic core; Max %LRNC, maximum per cent LRNC area.

Figure 3 Representative case of a 65-year-old male patient with sudden onset of right lower extremity weakness 1 month ago. (A and F) The curve planar reformatted images of the right and left CAs, respectively. The MR-VWI showed a high-risk plaque with large IPH (patchy hyperintense on 3D TOF (B), T1W (C), T2W (D), and MP-RAGE (E) images) in the left CA. In the same patient, a high-risk plaque with small focal IPH was observed in the right CA (displayed in the corresponding sequence images (G-J)). *Indicates the lumen. 3D TOF, three-dimensional time-of-flight; CA, carotid artery; IPH, intraplaque haemorrhage; JV, jugular vein; MP-RAGE, magnetisation-prepared rapid acquisition gradient-echo; MR-VWI, magnetic resonance vessel wall imaging; T1W, T1-weighted; T2W, T2-weighted. JV, jugular vein.
study had BCPs, and a paired comparison analysis was performed to compare the differences in plaque burden and components of the bilateral CAs. Our study also found that the plaque burden (mean lumen area, mean wall area and mean total vessel area) was significantly larger in the left CA than in the right CA. That is, the degree of positive remodelling was higher in the left CA than in the right CA. The differences in plaque burden between bilateral CAs may be explained by geometric factors, such as the bifurcation angle, and configuration of the left CA to the aortic arch as opposed to the right CA which arises from the brachiocephalic artery. Vessel anatomy in turn influences the haemodynamic forces and flow patterns and as such the left CA may be exposed to higher arterial pressures. Wall shear stress and stress inside the vessel wall may affect plaque formation and composition by causing alterations in the wall structure and metabolism.

Plaque evolution to an advanced lesion is associated with local factors. The interplay between the CA anatomy and the genesis of abnormal haemodynamics plays a role in atherosclerosis. Atherosclerosis progresses both as slow, gradual enlargement of the focal plaque and as a more dynamic process with periodic abrupt changes in microenvironmental components within the plaque. For example, the activated macrophages are recognised as an important hallmark of the inflammatory microenvironment in the atheroma. Macrophages express several different polarisation phenotypes and exert manifold effects in lesion development. Thus, the different expressions of cytokines, molecules and other biomarkers that characterise the microenvironment of each carotid plaque may contribute to this asymmetry of BCPs in the same patient. In patients with a specific vulnerable plaque component present in at least one side of the CA, the prevalence of LRNC was slightly higher in the left CA than in the right CA. While CVRFs could greatly affect the formation of lipids in the early stage of atherosclerosis, local factors may accelerate lipid accumulation during plaque progression, resulting in differences in LRNC between bilateral CAs. This might also be the reason for the higher prevalence of LRNC in the left CA.

IPH is one of the key features of vulnerable carotid plaques and contributes to LRNC enlargement and rapid plaque progression. In this study, IPH volumes were quantitatively analysed and compared in patients with coexisting IPH in BCPs, and the IPH volume in the left CA was significantly larger than that in the right CA. The difference in IPH volumes in the BCPs was probably due to haemodynamic forces, the density of the vasa vasorum and the substantial variation in the susceptibility of different parts of the arterial tree to various risk factors of atherosclerosis. A study found that previous use of antiplatelet agents was associated with carotid IPH on MRI. In the present study, the pairwise comparison between BCP characteristics in the same patient may have reduced possible interindividual bias, such as previous use of antiplatelet agents. It is unclear whether there are differences in the effects of antiplatelet agents on atherosclerotic plaques in different vascular beds of the same patient. A prospective study may help clarify this matter in the future.

This study has some limitations. First, this was a cross-sectional study. Thus, prospective studies are needed to investigate the characteristics of the dynamic progression of atherosclerosis in BCPs. Second, we only used MR-VWI to evaluate the features of BCPs without clarifying its correlation with pathological findings. Relevant pathological studies are needed to confirm our findings in the future. Third, we hypothesised that local factors would lead to differences in BCP burden and components, which is a pathological mechanism that requires further investigation. Finally, we only evaluated the differences between BCPs. It is worth noting that left-sided strokes might be recognised better or perceived as more severe, whereas right-sided strokes might be missed. This is one reason the prevalence of stroke is higher in the left hemisphere than in the right hemisphere. Further studies should be conducted to assess the impact of differences in BCPs on the prevalence of ischaemic stroke in both cerebral hemispheres.

CONCLUSIONS

Our study found differences in plaque burden and components between bilateral CAs in patients with BCPs. Compared with the right carotid plaque, the left carotid plaque was more likely to have larger plaque burden, higher prevalence of LRNC and greater IPH volume, which may contribute to the lateralisation of ischaemic stroke in the cerebral hemispheres.

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Acknowledgements We thank all the CARE-II investigators for their contributions to patient recruitment. We also thank Wang Kai from the Department of Nuclear Medicine, Beijing Tiantan Hospital, Capital Medical University, and Zhang Nan from the Department of Radiology, Beijing Anzhen Hospital, Capital Medical University, for their assistance with the language proof of this manuscript.

Contributors SS and HS analysed and interpreted patient data and drafted the manuscript. GW (the guarantor) and XZ contributed substantially to the conception and design of the study. RL and CY contributed substantially to interpretation and technical assistance. QS, BY, HW and DSH contributed to data interpretation and critically revised the manuscript. All authors read and approved the final manuscript.

Funding This study has received funding through grant from the Ministry of Health Commission of Shandong Province (202009010617).

Competing interests None declared.
Patient consent for publication  Not required.

Ethics approval  This study involves human participants and the study protocol was approved by the Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University and other local ethics committees at each participating hospital. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review  Not commissioned; externally peer reviewed.

Data availability statement  Data are available upon reasonable request.

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