![SVN Stroke & Vascular Neurology]

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

Sai Shao [ID],[1] Honglu Shi,[2] Guangbin Wang [ID],[1] Rui Li,[3] Qinjian Sun,[4] Bin Yao,[5] Hiroko Watase [ID],[6] Daniel S Hippe,[7] Chun Yuan,[7] Xihai Zhao [ID],[3] Investigators of CARE-II study

![Check for updates]

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=0.025), 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)

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Magnetic resonance vessel wall imaging can accurately characterise bilateral carotid plaques (BCPs), which may account for the lateralisation of ischaemic cerebral infarctions.

WHAT THIS STUDY ADDS

⇒ The characteristics of BCPs are different and may be influenced by local factors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The plaque on the left carotid artery deserves more attention due to its larger burden, more prevalent lipid-rich necrotic core and greater intraplaque haemorrhage volume.

---

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
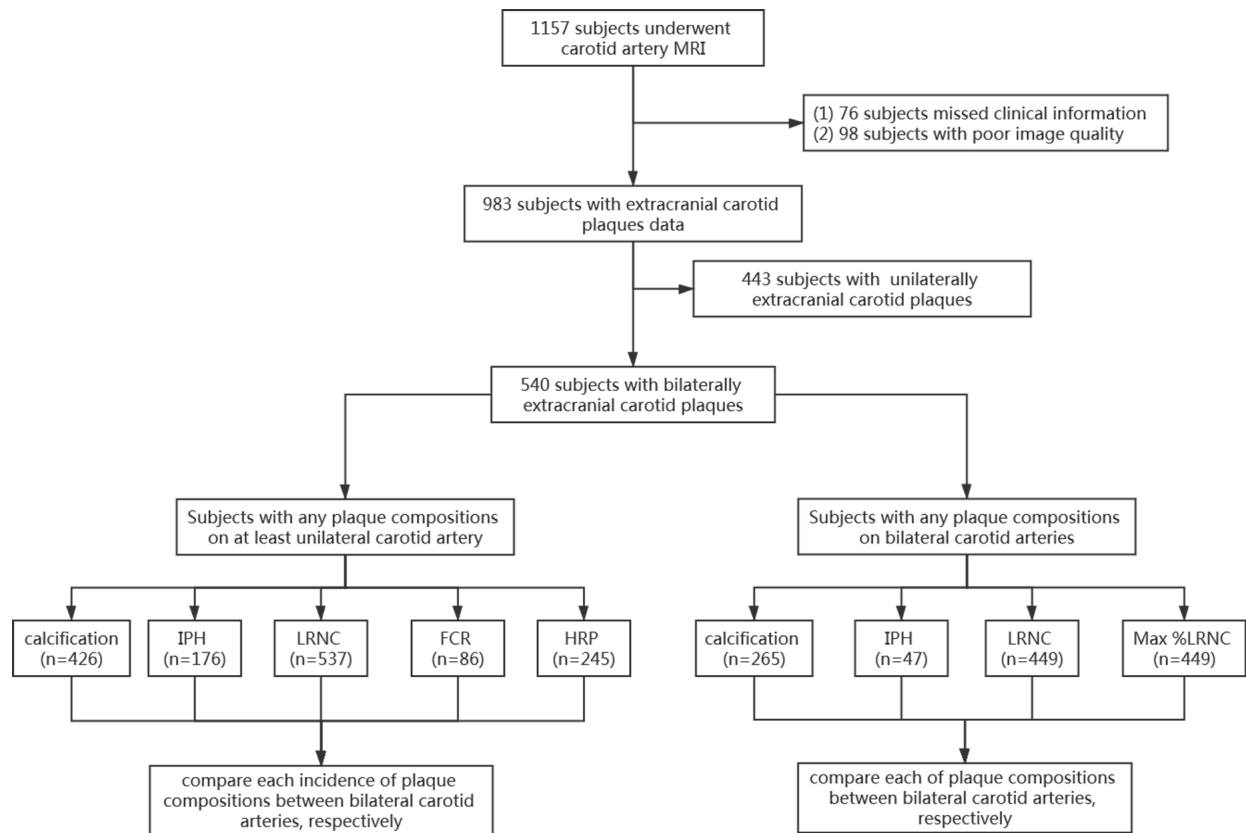
Figure 1 Flow chart of patient recruitment. FCR, fibrous cap rupture; HRP, high-risk plaque; IPH, intraplaque haemorrhage; LRNC, lipid-rich necrotic core.

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 ≥90 mm Hg or systolic blood pressure ≥140 mm Hg and/or use of antihypertensive agents. Diabetes was defined as fasting serum glucose levels ≥7.0 mmol/L and/or use of antidiabetic therapy. Hyperlipidaemia was defined as serum total cholesterol ≥5.17 mmol/L and/or triglycerides ≥1.7 mmol/L and/or high-density lipoprotein ≤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,

Table 1 Imaging parameters of the standardised multicontrast MR-VWI protocol

	TOF	T1W	T2W	MP-RAGE
Sequence	FFE	TSE	TSE	FFE
Black blood	None	QIR	MDIR	MSDE
Repeat time, ms	20	800	4800	8.8
Echo time, ms	4.9	10	50	5.3
Flip angle (°)	20	90	90	15
Field of view, cm	14×14	14×14	14×14	14×14
Matrix	256×256	256×256	256×256	256×256
Scan plane	Axial	Axial	Axial	Axial
Slice thickness, mm	1	2	2	1

FFE, fast field echo; MDIR, multislice double inversion recovery; MP-RAGE, magnetisation-prepared gradient recalled echo; MR-VWI, magnetic resonance vessel wall imaging; MSDE, motion sensitised-driven equilibrium; QIR, quadruple inversion recovery; TOF, time-of-flight; TSE, turbo spin echo; T1W, T1-weighted; T2W, T2-weighted.

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 ($140 \times 140 \, mm^2$) 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).[17] 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.[18] 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.[14 19] 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 vol/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%.[20] 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).[15 21]

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 means, the Wilcoxon signed-rank 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

Table 2 Clinical characteristics of symptomatic patients with concurrent bilateral carotid plaques (N=540)

Clinical characteristics	Mean±SD or n (%)
Age, years	65.6±9.9
Sex, male	411 (76.1)
Body mass index, kg/m^2	24.4±3.0
Smoke	314 (58.1)
Hypertension	431 (79.8)
Systolic blood pressure, mm Hg	143.8±21.5
Diastolic blood pressure, mm Hg	86.4±12.8
Hyperlipidaemia	298 (55.2)
Low-density lipoprotein, mmol/L	2.8±0.9
High-density lipoprotein, mmol/L	1.1±0.4
Total cholesterol, mmol/L	4.4±1.0
Triglycerides, mmol/L	1.7±1.0
Statin use	220 (40.7)
Diabetes	173 (32.0)
Coronary heart disease	97 (18.0)

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 mm^2 vs 41.2±14.5 mm^2, p<0.001), mean wall area (35.3±12.1 mm^2 vs 34.3±11.9 mm^2, p=0.025) and mean total vessel area (80.0±21.2 mm^2 vs 75.5±20.7 mm^2, 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 mm^3 vs 24.62±52.48 mm^3, p=0.146), LRNC volume (n=449; 108.9±171.9 mm^3 vs 114.1±183.9 mm^3, 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 mm^3 vs 87.5±106.0 mm^3, 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

Table 3 Comparisons of bilateral plaque burden in patients with BCPs (N=540)

	Mean±SD or n (%)		
	Left carotid artery	Right carotid artery	P value
Mean lumen area, mm^2	44.6±15.2	41.2±14.5	0.001
Mean wall area, mm^2	35.3±12.1	34.3±11.9	0.025
Mean total vessel area, mm^2	80.0±21.2	75.5±20.7	0.001
Mean wall thickness, mm	1.3±0.4	1.3±0.4	0.905
Normalised wall index, %	44.5±9.4	45.6±9.6	0.006
Moderate-to-severe stenosis	100 (18.5)	83 (15.4)	0.168

The mean lumen area and the mean total vessel area of the left carotid artery were significantly larger than those of the right carotid artery in symptomatic patients with BCPs.
BCPs, concurrent bilateral carotid plaques.

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

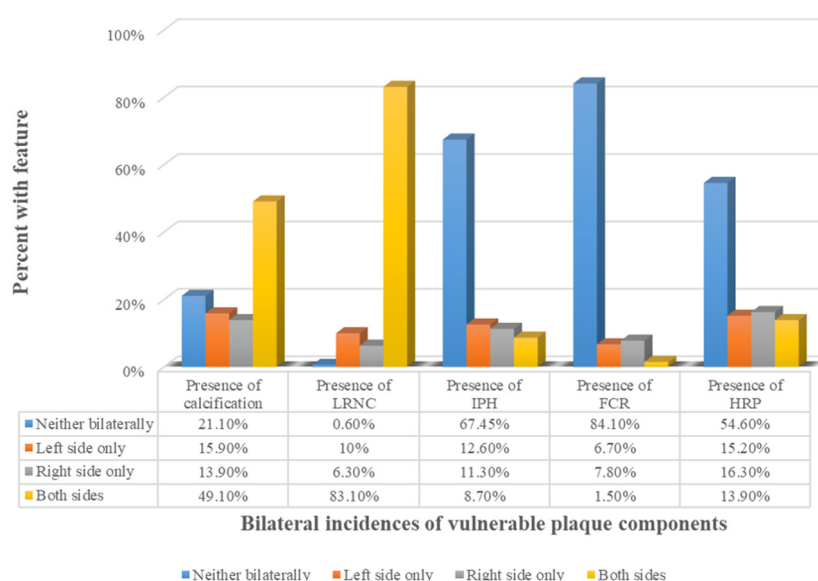|	n (%)				
		Present in at least one side			
	Neither bilaterally	**Left side only**	**Right side only**	**Both sides**	**P value†**
Presence of calcification	114 (21.1)	426 (78.9)			0.382
		86 (15.9)	75 (13.9)	265 (49.1)	
Presence of LRNC	3 (0.6)	537 (99.4)			0.026*
		54 (10.0)	34 (6.3)	449 (83.1)	
Presence of IPH	364 (67.4)	176 (32.6)			0.439
		68 (12.6)	61 (11.3)	47 (8.7)	
Presence of FCR	454 (84.1)	86 (15.9)			0.358
		36 (6.7)	42 (7.8)	8 (1.5)	
Presence of HRP	295 (54.6)	245 (45.4)			0.485
		82 (15.2)	88 (16.3)	75 (13.9)	

*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).
BCPs, concurrent bilateral carotid artery plaques; FCR, fibrous cap rupture; HRP, high-risk plaque; IPH, intraplaque haemorrhage; LRNC, lipid-rich necrotic core.

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.[15] 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%

	Presence of calcification	Presence of LRNC	Presence of IPH	Presence of FCR	Presence of HRP
■ Neither bilaterally	21.10%	0.60%	67.45%	84.10%	54.60%
■ Left side only	15.90%	10%	12.60%	6.70%	15.20%
■ Right side only	13.90%	6.30%	11.30%	7.80%	16.30%
■ Both sides	49.10%	83.10%	8.70%	1.50%	13.90%

Bilateral incidences of vulnerable plaque components

■ Neither bilaterally ■ Left side only ■ Right side only ■ Both sides

Figure 2 Bilateral presence of vulnerable plaque features in symptomatic patients with BCP. BCPs, concurrent bilateral carotid artery plaque; FCR, fibrous cap rupture; HRP, high-risk plaque; IPH, intraplaque haemorrhage; LRNC, lipid-rich necrotic core.

Table 5 Comparison of concurrent vulnerable plaque components bilaterally in symptomatic patients with BCPs

	Mean±SD		
	Left carotid artery	Right carotid artery	P value
Volume of calcification, mm^3	25.3±48.5	24.62±52.48	0.146
Volume of LRNC, mm^3	108.9±171.9	114.1±183.9	0.337
Volume of IPH, mm^3	148.4±168.3	87.5±106.0	0.011*
Max %LRNC, %	23±18	24±19	0.242

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

of patients with ischaemic stroke.[22] In our previous study, 19% of participants had plaques with ≥50% carotid stenosis.[18] A similar prevalence was found in Taiwanese (>50% stenosis: 13%)[23] and Hong Kong (>50% stenosis: 18%)[24] 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.[25] Compared with their findings, our outcomes showed that LRNC was more prevalent in the left CA, while the prevalence of IPH was similar between

BCPs. Interestingly, when performing quantitative analysis, the IPH volume was significantly larger in the left CA. The reason for these differences may be that our study design differed from that of Selwaness et al,[26] who compared plaque burden and components between left-sided and right-sided unilateral plaques. Further, their cohort was population-based in Rotterdam, whereas our cohort was patient-based in China. Differences in race, geography and prevalence of stroke may have contributed to the differences in the results between the two studies. Moreover, Li and Wang[27] reported bilateral symmetry of human CA plaques, and even weak symmetry of IPH and CA scores, and concluded that plaque morphology, calcification and LRNC may develop symmetrically. When they assessed the associations of volume measurements between BCPs, the results showed a relatively poor correlation for lipid content and a weak symmetry of IPH between sides. Their results corroborate our results to some extent. However, compared with our study, their sample size was relatively smaller (n=177); some patients had only unilateral carotid plaque and the CVRFs differed among patients. These may have contributed to some bias in the comparison of plaque burden and components in the bilateral CAs. In contrast, all patients included in our
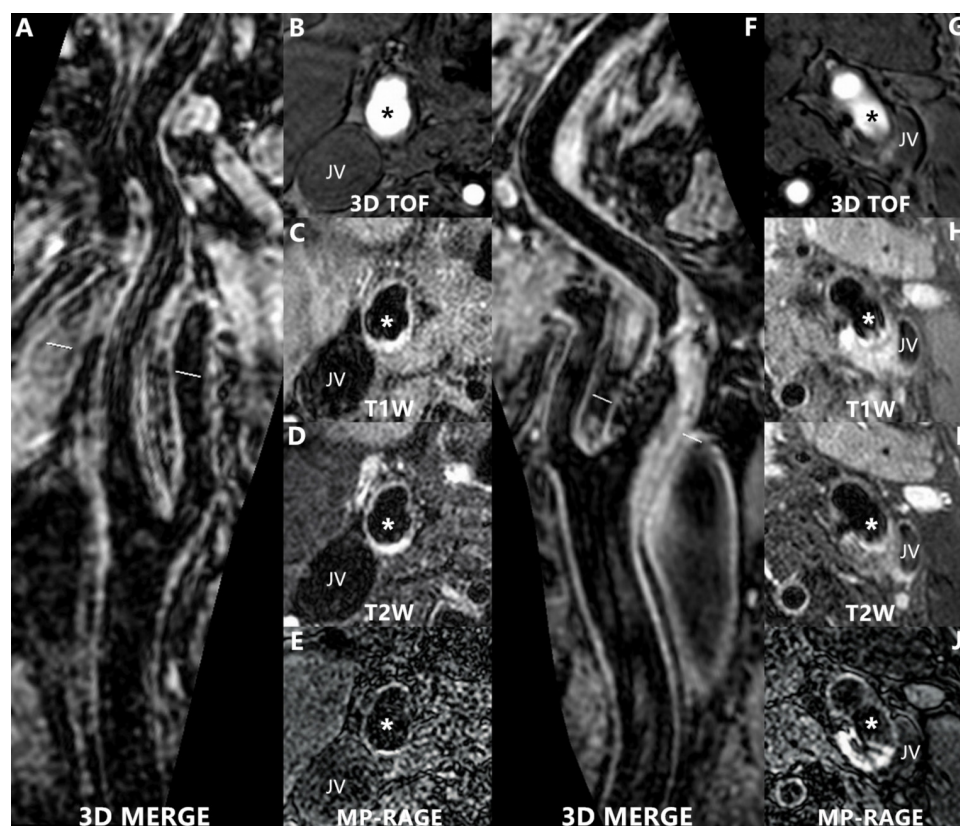
Figure 3 Representative case of a 65-year-old male patient with sudden onset of right lower extremity weakness 1 month ago. (A and F) The curve planar reformation images of the right and left CAs, respectively. The MR-VWI showed a high-risk plaque with large IPH (patchy hyperintense on 3D TOF (B), T1W (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.[25] Vessel anatomy in turn influences the haemodynamic forces and flow patterns and as such the left CA may be exposed to higher arterial pressures.[10 28] Wall shear stress and stress inside the vessel wall may affect plaque formation and composition by causing alterations in the wall structure and metabolism.[29 30]

Plaque evolution to an advanced lesion is associated with local factors.[27] The interplay between the CA anatomy and the genesis of abnormal haemodynamics plays a role in atherosclerosis.[10] 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.[31] 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.[32] 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.[27 33] 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.[26 34] 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.[9] A study found that previous use of antiplatelet agents was associated with carotid IPH on MRI.[35] 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.[36] 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.

Author affiliations
[1]Department of Radiology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China
[2]Department of Medical Imaging and Intervention, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China
[3]Center for Biomedical Imaging Research, Department of Biomedical Engineering, Tsinghua University School of Medicine, Beijing, China
[4]Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China
[5]Department of Radiology, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China
[6]Department of Surgery, University of Washington, Seattle, Washington, USA
[7]Department of Radiology, University of Washington, Seattle, Washington, USA

ORCID iDs
Sai Shao http://orcid.org/0000-0002-4190-5493
Guangbin Wang http://orcid.org/0000-0001-7410-5540
Hiroko Watase http://orcid.org/0000-0002-8951-7692
Xihai Zhao http://orcid.org/0000-0001-8953-0566

REFERENCES

1 Ooi YC, Gonzalez NR. Management of extracranial carotid artery disease. *Cardiol Clin* 2015;33:1–35.
2 Millon A, Mathevet J-L, Boussel L, et al. High-resolution magnetic resonance imaging of carotid atherosclerosis identifies vulnerable carotid plaques. *J Vasc Surg* 2013;57:1046–51.
3 Grimm JM, Schindler A, Freilinger T, et al. Comparison of symptomatic and asymptomatic atherosclerotic carotid plaques using parallel imaging and 3 T black-blood in vivo CMR. *J Cardiovasc Magn Reson* 2013;15:44.
4 Yamada K, Kawasaki M, Yoshimura S, et al. High-intensity signal in carotid plaque on routine 3d-TOF-MRA is a risk factor of ischemic stroke. *Cerebrovasc Dis* 2016;41:13–18.
5 Rodríguez Hernández SA, Kroon AA, van Boxtel MPJ, et al. Is there a side predilection for cerebrovascular disease? *Hypertension* 2003;42:56–60.
6 Naess H, Waje-Andreassen U, Thomassen L, et al. High incidence of infarction in the left cerebral hemisphere among young adults. *J Stroke Cerebrovasc Dis* 2006;15:241–4.
7 Foerch C, Misselwitz B, Sitzer M, et al. Difference in recognition of right and left hemispheric stroke. *Lancet* 2005;366:392–3.
8 Hedna VS, Bodhit AN, Ansari S, et al. Hemispheric differences in ischemic stroke: is left-hemisphere stroke more common? *J Clin Neurol* 2013;9:97–102.
9 Poredos P, Poredos P, Jezovnik MK. Structure of atherosclerotic plaques in different vascular territories: clinical relevance. *Curr Vasc Pharmacol* 2018;16:125–9.
10 Phan TG, Beare RJ, Jolley D, et al. Carotid artery anatomy and geometry as risk factors for carotid atherosclerotic disease. *Stroke* 2012;43:1596–601.
11 Lee S-W, Antiga L, Spence JD, et al. Geometry of the carotid bifurcation predicts its exposure to disturbed flow. *Stroke* 2008;39:2341–7.
12 Thomas JB, Antiga L, Che SL, et al. Variation in the carotid bifurcation geometry of young versus older adults: implications for geometric risk of atherosclerosis. *Stroke* 2005;36:2450–6.
13 Zhao X, Li R, Hippe DS, et al. Chinese atherosclerosis risk evaluation (care II) study: a novel cross-sectional, multicentre study of the prevalence of high-risk atherosclerotic carotid plaque in Chinese patients with ischaemic cerebrovascular events-design and rationale. *Stroke Vasc Neurol* 2017;2:15–20.
14 Cai J-M, Hatsukami TS, Ferguson MS, et al. Classification of human carotid atherosclerotic lesions with in vivo multicontrast magnetic resonance imaging. *Circulation* 2002;106:1368–73.
15 Saam T, Ferguson MS, Yarnykh VL, et al. Quantitative evaluation of carotid plaque composition by in vivo MRI. *Arterioscler Thromb Vasc Biol* 2005;25:234–9.
16 Gupta A, Baradaran H, Schweitzer AD, et al. Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. *Stroke* 2013;44:3071–7.
17 Kerwin W, Xu D, Liu F, et al. Magnetic resonance imaging of carotid atherosclerosis: plaque analysis. *Top Magn Reson Imaging* 2007;18:371–8.
18 North American Symptomatic Carotid Endarterectomy Trial Collaborators, Barnett HJM, Taylor DW, et al. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325:445–53.
19 Chu B, Kampschulte A, Ferguson MS, et al. Hemorrhage in the atherosclerotic carotid plaque: a high-resolution MRI study. *Stroke* 2004;35:1079–84.
20 Zhao X, Hippe DS, Li R, et al. Prevalence and characteristics of carotid artery high-risk atherosclerotic plaques in Chinese patients with cerebrovascular symptoms: a Chinese atherosclerosis risk evaluation II study. *J Am Heart Assoc* 2017;6.
21 Cai Y, He L, Yuan C, et al. Atherosclerotic plaque features and distribution in bilateral carotid arteries of asymptomatic elderly population: a 3D multicontrast MR vessel wall imaging study. *Eur J Radiol* 2017;96:6–11.
22 Wang Y, Zhao X, Liu L, et al. Prevalence and outcomes of symptomatic intracranial large artery stenoses and occlusions in China: the Chinese intracranial atherosclerosis (CICAS) study. *Stroke* 2014;45:663–9.
23 Jeng JS, Chung MY, Yip PK, et al. Extracranial carotid atherosclerosis and vascular risk factors in different types of ischemic stroke in Taiwan. *Stroke* 1994;25:1989–93.
24 Leung SY, Ng TH, Yuen ST, et al. Pattern of cerebral atherosclerosis in Hong Kong Chinese. Severity in intracranial and extracranial vessels. *Stroke* 1993;24:779–86.
25 Selwaness M, van den Bouwhuijsen Q, van Onkelen RS, et al. Atherosclerotic plaque in the left carotid artery is more vulnerable than in the right. *Stroke* 2014;45:3226–30.
26 Selwaness M, Bos D, van den Bouwhuijsen Q, et al. Carotid atherosclerotic plaque characteristics on magnetic resonance imaging relate with history of stroke and coronary heart disease. *Stroke* 2016;47:1542–7.
27 Li F, Wang X. Bilateral symmetry of human carotid artery atherosclerosis: a multi-contrast weighted MR study. *Int J Cardiovasc Imaging* 2016;32:1219–26.
28 Schulz UG, Rothwell PM. Major variation in carotid bifurcation anatomy: a possible risk factor for plaque development? *Stroke* 2001;32:2522–9.
29 Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. *JAMA* 1999;282:2035–42.
30 Chatzizisis YS, Jonas M, Coskun AU, et al. Prediction of the localization of high-risk coronary atherosclerotic plaques on the basis of low endothelial shear stress: an intravascular ultrasound and histopathology natural history study. *Circulation* 2008;117:993–1002.
31 Yurdagul A, Finney AC, Woolard MD, et al. The arterial microenvironment: the where and why of atherosclerosis. *Biochem J* 2016;473:1281–95.
32 Yunna C, Mengru H, Lei W, et al. Macrophage M1/M2 polarization. *Eur J Pharmacol* 2020;877:173090.
33 VanderLaan PA, Reardon CA, Getz GS. Site specificity of atherosclerosis: site-selective responses to atherosclerotic modulators. *Arterioscler Thromb Vasc Biol* 2004;24:12–22.
34 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;268:61–8.
35 Liem MI, Schreuder FHBM, van Dijk AC, et al. Use of antiplatelet agents is associated with intraplaque hemorrhage on carotid magnetic resonance imaging: the plaque at risk study. *Stroke* 2015;46:3411–5.
36 Portegies MLP, Selwaness M, Hofman A, et al. Left-sided strokes are more often recognized than right-sided strokes: the rotterdam study. *Stroke* 2015;46:252–4.