EXTRA
Cerebrovascular Diseases

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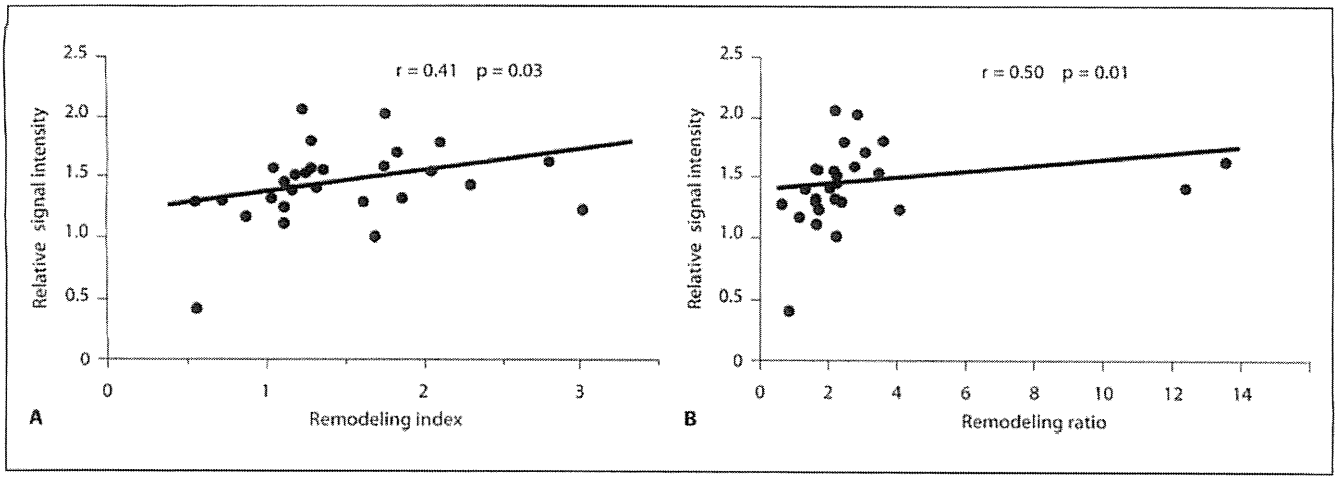

Fig. 3. Correlations between rSI and RI (**A**)/RR (**B**) were calculated, and significant correlations were found between both RI and rSI (r = 0.41, p = 0.03), and between RR and rSI (r = 0.50, p = 0.01).

Discussion

This study demonstrated three main findings. Firstly, plaques in the carotid artery with positive remodeling were associated with a significantly higher stroke prevalence than plaques with negative remodeling. Secondly, plaques with positive remodeling appeared to have significantly higher lipid contents than those with negative remodeling in both radiologic and histologic analysis. We also demonstrated that levels of biological markers, such as hsCRP, HbA1C, total cholesterol, LDL-C and HDL-C, were not useful for predicting stroke events, even though they have been shown to be significantly associated with coronary events [8].

Extensive vascular remodeling in the coronary circulation may be an indicator of plaque vulnerability to rupture [4]. Vulnerable plaques may contain a large necrotic lipid core with a thin or disrupted fibrous cap, with the potential to cause embolization or thrombosis. A previous report also found that plaques with positive remodeling had significantly larger lipid cores and higher macrophage counts than negatively or less positively remodeled plaques, also indicating increased vulnerability of more extensively remodeled plaques using a combination of functional and morphologic mechanisms [6].

MDCT angiography can clearly depict the various layers constituting the arterial wall. This technique has previously been used as an accurate method of assessing the percent luminal narrowing in the carotid artery [19]. The curved multiplanar reconstruction analysis technique used in the current study has the advantage of being able to evaluate luminal narrowing throughout the carotid artery, making identification of the point of maximum narrowing easier. A previous study proposed two potentially useful parameters for demonstrating the degree of arteriosclerosis in the coronary artery. The plaque RI is calculated as the ratio of CSA at the point of maximal vessel stenosis, measured from the luminal-intimal boundary to the outer vessel wall, to the mean reference CSA [17]. The plaque RR is calculated as the ratio of CSA at the point of maximal vessel stenosis to the reference CSA at the distal portion [18]. RR is similar to the use of NASCET criteria to assess the degree of luminal narrowing. RI is less likely to be subject to artificial variation (compared with RR) and might thus represent a more stable and accurate assessment scale. In the current study, we calculated correlations using both measures to exclude any discrepancies

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Table 3. Comparison of radiologic parameters between type-VI and non-type-VI groups (means ± SD)

Variables	Type-VI group	Non-type-VI group	p value
Lesions, n	5	5	
Age, years	66.4 ± 5.32	67.2 ± 5.26	>0.05
NASCET, %	76.5 ± 11.7	74.9 ± 9.5	>0.05
RI	1.35 ± 0.34	0.88 ± 0.25	<0.05
RR	2.29 ± 0.49	1.30 ± 0.33	<0.05
rSI on T1WI	1.50 ± 0.15	1.07 ± 0.38	<0.05

Table 4. Comparison of biological markers between symptomatic and asymptomatic groups (means ± SD)

Markers	Symptomatic (n = 17)	Asymptomatic (n = 11)	p value
hsCRP, mg/dl	0.18 ± 0.21	0.25 ± 0.30	>0.05
T-Chol, mg/dl	180.3 ± 37.7	165.9 ± 30.3	>0.05
HDL-C, mg/dl	48.3 ± 13.6	42.0 ± 11.6	>0.05
LDL-C, mg/dl	105.7 ± 34.2	104.2 ± 27.0	>0.05
HbA1c, %	6.2 ± 0.76	7.0 ± 2.18	>0.05

T-Chol = Total cholesterol.

associated with the analytical method, and the results suggested that positive RR and RI values were both predictive of stroke events, as in coronary arteries. These results are in accord with those of another recent report, which showed that a positive RR value indicated underlying atherosclerotic plaque vulnerability in carotid arteries using MDCT angiography [9].

A previous study of positive remodeling of the internal carotid artery was limited by the lack of correlations between histologic vessel wall measurements and MDCT values [9]. Complicated and vulnerable plaques are defined by histologic analysis as plaques with surface rupture or intraplaque/intraluminal hemorrhage, indicative of stage VI by histologic AHA criteria [20]. Previous reports demonstrated that T1WI of carotid arteries may be useful for identifying histologically complicated plaques with hemorrhage or thrombus, because the formation of methemoglobin is associated with shortening of T_1 in the acute to subacute phase of rupture [21]. Furthermore, new MRI techniques may be able to differentiate between atherosclerotic plaques in terms of the presence of lipid-rich necrotic cores, hemorrhage and calcification [22]. In the current study, the qualitative contents of plaques were estimated using the BB technique, suppressing the signal from flowing blood, based on pulse sequences designed for vascular imaging [13]. These sequences are ideal for plaque imaging because the conspicuity of the vessel wall is increased when adjacent to a hypointense lumen, in which the echo and repetition times can be varied to optimize visualization of specific plaque components [23]. The ratio of plaque intensity to that of the sternocleidomastoid muscle was calculated to eliminate variations in intensity among images [14]. Our results showed that rSI was higher in symptomatic than in asymptomatic plaques. We also confirmed that rSI correlated significantly with both RI and RR. These results suggest that

plaques in positively remodeled internal carotid arteries, indicative of type VI stage by AHA criteria, may be more vulnerable to stroke than those in arteries with luminal narrowing. Thus, combined analysis of both RI and RR using MDCT angiography and rSI using BB MRI may be useful for predicting stroke events. We confirmed the validity of this conclusion by histologic analysis of plaques obtained by CEA. The indications for surgical interventions, including CEA and CAS, might be reconsidered on the basis of histologic alterations, represented by RI, RR or rSI, because low-grade stenosis with vulnerable lesions may result in cerebrovascular events [24].

Numerous potential risk factors for the development of atherosclerotic plaques in coronary events have been reported [8]. hsCRP, in particular, has been focused on as an independent risk factor for ischemic stroke in Japanese men [25]. In the current study, we calculated the correlations between the degree of positive remodeling and levels of hsCRP, HbA1C, total cholesterol, LDL-C and HDL-C; however, the results suggested that these markers were of little value in predicting future stroke events.

This study had several potential limitations. First, the retrospective design of the study meant that the parameters being measured could be the results, rather than the causes of the cerebral events. In addition, although the assessed plaques may have been the source of the symptoms, imaging only assessed a representative selection of previously ruptured plaques. These factors imply that it is difficult to draw firm conclusions about the predictive value of remodeling parameters for future stroke events. Secondly, the number of patients assessed in this study was small and further prospective studies with more patients are needed to validate the results of this preliminary study.

Conclusions

In the current series of patients with significant carotid stenosis, the degree of positive remodeling, represented by both RI and RR, was significantly greater in symptomatic lesions with cerebral ischemic events than in asymptomatic lesions. In both radiologic and histologic analyses, these lesions were confirmed as vulnerable plaques with underlying surface rupture or intraplaque/intraluminal hemorrhage, indicative of stage VI according to histologic AHA criteria. These results suggest that the combined analysis of RR, RI and rSI might help to predict future stroke events.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

1 Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991;325:445–453.
2 Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, Rankin RN, Clagett GP, Hachinski VC, Sackett DL, Thorpe KE, Meldrum HE, Spemce JD: Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1998;339:1415–1425.

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3 Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, Balwa TK, Whitlow P, Strickman NE, Jaf MR, Popma JJ, Snead DB, Cutlip DE, Firth BG, Ouriel K, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators: Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004;351:1493–1501.
4 Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ: Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371–1375.
5 Schoenhagen P, Ziada KM, Kapadia SR, Crowe TD, Nissen SE, Tuzcu EM: Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: an intravascular ultrasound study. Circulation 2000;101:598–603.
6 Varnava AM, Mills PG, Davies MJ: Relationship between coronary artery remodeling and plaque vulnerability. Circulation 2002;105:939–943.
7 Kiechl S, Willeit J: The natural course of atherosclerosis. Part I: incidence and progression. Arterioscler Thromb Vasc Biol 1999;19:1484–1490.
8 Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, Fayad Z, Stone PH, Waxman S, Raggi P, Madjid M, Zarrabi A, Burke A, Yuan C, Fitzgerald PJ, Siscovick DS, de Korte CL, Aikawa M, Juhani Airaksinen KE, Assmann G, Becker CR, Chesebro JH, Farb A, Galis ZS, Jackson C, Jang IK, Koening W, Lodder RA, March K, Demirovic J, Navab M, Priori SG, Rekhter MD, Bahr R, Grundy SM, Mehran R, Colombo A, Boerwinkle E, Ballantyne C, Insull W Jr, Schwartz RS, Vogel R, Serruys PW, Hansson GK, Faxon DP, Kaul S, Drexler H, Greenland P, Muller JE, Virmani R, Ridker PM, Zipes DP, Shah PK, Willerson JT: From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies. Part I. Circulation 2003;108:1664–1672.
9 Hardie AD, Kramer CM, Raghavan P, Baskurt E, Nandalur KR: The impact of expansive arterial remodeling on clinical presentation in carotid artery disease: a multidetector CT angiography study. AJNR Am J Neuroradiol 2007;28:1067–1070.
10 Saba L, Sanfilippo R, Pirisi R, Pascalis L, Montisci R, Mallarini G: Multidetector-row CT angiography in the study of atherosclerotic carotid arteries. Neuroradiology 2007;49:623–637.
11 Coombs BD, Rapp JH, Ursell PC, Reilly LM, Saloner D: Structure of plaque at carotid bifurcation: high-resolution MRI with histological correlation. Stroke 2001;32:2516–2521.
12 Gortler M, Goldmann A, Mohr W, Widder B: Tissue characterisation of atherosclerotic carotid plaques by MRI. Neuroradiology 1995;37:631–635.
13 Simonetti OP, Finn JP, White RD, Laub G, Henry DA: 'Black blood' T2-weighted inversion-recovery MR imaging of the heart. Radiology 1996;199:49–57.
14 Yoshida K, Narumi O, Chin M, Inoue K, Tabuchi T, Oda K, Nagayama M, Egawa N, Hojo M, Goto Y, Watanabe Y, Yamagata S: Characterization of carotid atherosclerosis and detection of soft plaque with use of black-blood MR imaging. AJNR Am J Neuroradiol 2008;29:868–874.
15 Albers GW, Caplan LR, Easton JD, Fayad PB, Mohr JP, Saver JL, Sherman DG, TIA Working Group: Transient ischemic attack – proposal for a new definition. N Engl J Med 2002;347:1713–1716.
16 Inzitari D, Eliasziw M, Gates P, Sharpe BL, Chan RK, Meldrum HE, Barnett HJ: The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 2000;342:1693–1700.
17 Imazeki T, Sato Y, Inoue F, Anazawa T, Tani S, Matsumoto N, Takayama T, Uchiyama T, Saito S: Evaluation of coronary artery remodeling in patients with acute coronary syndrome and stable angina by multislice computed tomography. Circ J 2004;68:1045–1050.
18 Achenbach S, Ropers D, Hoffmann U, MacNeill B, Baum U, Pohle K, Brady TJ, Pomerantsev E, Ludwig J, Flachskampf FA, Wicky S, Jang IK, Daniel WG: Assessment of coronary remodeling in stenotic and nonstenotic coronary atherosclerotic lesions by multidetector spiral computed tomography. J Am Coll Cardiol 2004;43:842–847.
19 Randoux B, Marro B, Koskas F, Duyme M, Sahel M, Zouaoui A, Marsault C: Carotid artery stenosis: prospective comparison of CT, three-dimensional gadolinium-enhanced MR, and conventional angiography. Radiology 2001;220:179–185.
20 Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull W Jr, Rosenfeld ME, Schwartz CJ, Wagner WD, Wissler RW: A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation 1995;92:1355–1374.

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www.karger.com/cee

21 Moody AR, Murphy RE, Morgan PS, Martel AL, Delay GS, Allder S, MacSweeney ST, Tennant WG, Gladman J, Lowe J, Hunt BJ: Characterization of complicated carotid plaque with magnetic resonance direct thrombus imaging in patients with cerebral ischemia. Circulation 2003;107:3047–3052.
22 Yuan C, Kerwin WS, Yarnykh VL, Cai J, Saam T, Chu B, Takaya N, Ferguson MS, Underhill H, Xu D, Liu F, Hatsukami TS: MRI of atherosclerosis in clinical trials. NMR Biomed 2006;19:636–654.
23 Chu B, Kampschulte A, Ferguson MS, Kerwin WS, Yarnykh VL, O'Brien KD, Polissar NL, Hatsukami TS, Yuan C: Hemorrhage in the atherosclerotic carotid plaque: a high-resolution MRI study. Stroke 2004;35:1079–1084.
24 Virmani R, Ladich ER, Burke AP, Kolodgie FD: Histopathology of carotid atherosclerotic disease. Neurosurgery 2006;59(5 suppl 3):S219–S227, discussion S3–S13.
25 Wakugawa Y, Kiyohara Y, Tanizaki Y, Kubo M, Ninomiya T, Hata J, Doi Y, Okubo K, Oishi Y, Shikata K, Yonemoto K, Maebuchi D, Ibayashi S, Iida M: C-reactive protein and risk of first-ever ischemic and hemorrhagic stroke in a general Japanese population: the Hisayama Study. Stroke 2006;37:27–32.