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Lipid Core Plaque Distribution Using Near-infrared Spectroscopy Is Consistent with Pathological Evaluation in Carotid Artery Plaques

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Abstract

Carotid artery stenting (CAS) is performed as a treatment for carotid artery stenosis. However, lipid-rich plaques cause embolic complications and sequelae. Near-infrared spectroscopy (NIRS) can identify lipid components by applying a near-infrared absorption pattern, and the distribution of lipid components can be evaluated as the maximum lipid core burden index (maxLCBI). Intravascular ultrasound (IVUS) equipped with NIRS has been clinically applied recently, and its diagnostic usefulness and validation have been reported for coronary arteries; however, its consistency with actual pathological diagnosis in carotid artery lesions has not been validated. In this study, we investigated the consistency between the maxLCBI values and histopathological diagnoses. Patients with cervical carotid artery stenosis who underwent carotid endarterectomy (CEA) were examined in this prospective study. Pathological diagnosis was determined after NIRS evaluation, which was performed on the extracted plaques *ex vivo*. The histological slices of decalcified and paraffin-embedded sections were stained by hematoxylin–eosin (HE) and Elastica van Gieson (EVG), and for low-density lipoprotein (LDL), C-reactive protein (CRP), CD68, and glycophorin A. The correlation between maxLCBI values and histological findings. Seventy lesions assessed by NIRS were pathologically analyzed. There was a positive linear correlation between maxLCBI values and pathological findings as determined by HE (angle), HE (area%), EVG, CRP, and CD68 staining (respectively, $r = 0.624$, $p < 0.001$; $r = 0.578$, $p < 0.001$; $r = 0.534$, $p < 0.001$; $r = 0.723$, $p < 0.001$; $r = 0.653$, $p < 0.001$). In conclusion, the maxLCBI values assessed by NIRS showed a significant positive linear correlation with pathological evaluations in carotid lesions. The maxLCBI values in carotid arteries are consistent with pathological evaluations.

Keywords: imaging modalities, carotid artery stenosis, lipid plaque, NIRS-IVUS, carotid artery stenting

Introduction

As endovascular techniques and devices have advanced, carotid artery stenting (CAS) has become an alternative to carotid endarterectomy (CEA) for carotid artery stenosis. However, accurately evaluating preoperative plaque characteristics are essential because lesions with lipid-rich plaques put patients at risk of complications leading to sequelae in CAS.[1,2] Plaque protrusions (PP) appear in the lumen of stents after stenting in patients with lipid-rich carotid plaques, and PP is strongly correlated with perioperative ischemic complications.[1] Evaluation of plaque characteristics using magnetic resonance imaging (MRI) is commonly used to assess carotid plaques.[3–5] Recent quantitative color-coded T1-weighted MR plaque imaging for preoperative plaque diagnosis can accurately distinguish lipid core and intraplaque hemorrhages (IPHs)[5]; however, high-resolution MRI is not always an option for patients before

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revascularization.[6] An additional imaging modality that can accurately identify the lipid components of carotid plaque at high risk for embolic complications during CAS would be therefore required.

Near-infrared spectroscopy (NIRS) is a diagnostic imaging technique that can identify lipid components by applying a near-infrared absorption pattern that is different from that of other tissues.[7] Recently, an intravascular diagnostic imaging device using NIRS, NIRS-intravascular ultrasound (NIRS-IVUS), has been clinically applied. NIRS can accurately evaluate lipid core plaque (LCP) distributions, and a correlation between NIRS diagnosis and clinical prognosis in coronary artery lesions has been demonstrated.[8] Furthermore, a consistent relationship between NIRS evaluation and pathological diagnosis in coronary artery plaques has been found. According to comparisons with pathological coronary tissue in autopsy cases, the sensitivity of lipid plaque detection on NIRS is 90% and the specificity is 93%.[9] However, the consistency with actual pathological plaque diagnosis in carotid artery lesions has not been studied. The purpose of the present study was to investigate the consistency between evaluations of the lipid core distribution using NIRS and pathological findings for carotid plaque specimens.

Methods

Study population

From April 2018 to February 2020, consecutive patients with cervical carotid artery stenosis who underwent CEA were examined in this prospective study. The subjects were cases with carotid artery stenosis over 20 years old who underwent CEA for carotid stenosis with surgical indications according to the Japanese Guidelines for the Management of Stroke 2015 (Supplement 2019). All examinations in this study were performed after obtaining approval from the institutional review board (No. 1936) and written informed consent from each patient.

CEA procedure

All CEAs were performed under general anesthesia. A skin incision was performed at the forward edge of the sternocleidomastoid muscle to expose the common carotid artery, external carotid artery, and internal carotid artery for dissection around connecting tissues. The carotid plaque was carefully removed in a one-piece fashion without cutting inside through a fibrous cap (Fig. 1). For carotid plaque evaluation using NIRS-IVUS, the extracted specimens were excised without making an incision in the thickened intima and the lumen was kept intact to avoid plaque damage. After removal of the specimen, the incised carotid artery was sutured water-tightly with 3-0 GORE-TEX suture (W. L. Gore & Associates, Inc., Newark, DE, USA), and the operation was completed with meticulous hemostasis.

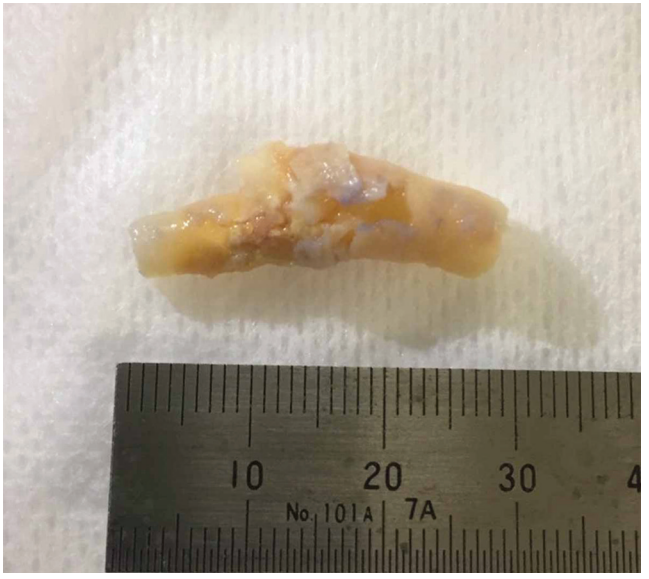

Fig. 1 The extracted carotid plaque in a one-piece fashion.

NIRS-IVUS procedure and maxLCBI analysis

Ex vivo NIRS-IVUS assessment of excised carotid plaque specimen was subsequently performed. First, the wrap was removed from the intimal plaque of the carotid artery with gauze and immersed in a container filled with saline. Second, a 3.2 F Infraredx NIRS catheter (InfraReDx, Burlington, MA, USA) was advanced along a 0.014-inch guidewire (GT wire; Terumo Medical, NJ, USA) through the plaque in saline. The catheter was connected to the TVC Imaging System (Makoto™; Infraredx), and the LCP was measured by automatic pullback at 0.5 mm/s. The proximal edge of the specimens was labeled as 0 mm and associated with the proximal histology thin section. To provide a quantitative summary metric of the LCP over the entire scanned segment, the maximum lipid core burden index (maxLCBI) was calculated. The chemogram displayed color-coded blocks according to the probability of finding a lipid plaque, if the percentage probability value for lipids was ≥0.98, the block showed yellow. LCBI is the fraction of LCP-positive area in the chemogram multiplied by 1000 for any 4mm segment. The maxLCBI was defined as the maximum value of the LCBI for any 4 mm segment. The maxLCBI was calculated based on the scanned segment every 4 mm including the minimal lumen area. After the measurement of the maxLCBI values, the specimen was pathologically evaluated.

Histological evaluation

Specimens excised from the carotid artery during CEA were provided for histological evaluation. After fixation by formaldehyde, each segment was cut perpendicular from the proximal side of each 5-mm interval of the plaque. The histological sections of decalcified and paraffin-embedded tissue were stained by hematoxylin–eosin (HE) and Elastica van Gieson (EVG). Serial sections were assessed by immunohistochemical stain using primary antibodies for oxidized low-density lipoprotein (LDL) (rabbit polyclonal antibody, Immundiagnostik AG, Bensheim, Germany), C-reactive protein (CRP) (clone CRP-8, Sigma-Aldrich, St. Louis, MO, USA), CD68 (clone PG-M1, Dako, Glostrup, Denmark), and glycophorin A (clone JC159, DakoCytomation, Carpinteria, CA, USA) using Envision methods as previously described.[10] Histopathological features of the plaque were analyzed based on the agreement of a pathologist (KH) who was blinded to the NIVUS and NIRS findings. The proportion of the lipid area was measured using NanoZoomer Digital Pathology ver. 2.7.43 (Hamamatsu Photonics K.K., Hamamatsu, Japan) for all sections stained by HE and EVG. In immunohistochemical staining sections, the ratio of the positive part to the total area was measured. In addition, to investigate the lipid distribution, the angle of lipid distribution from the center of the lumen was measured (Fig. 2).

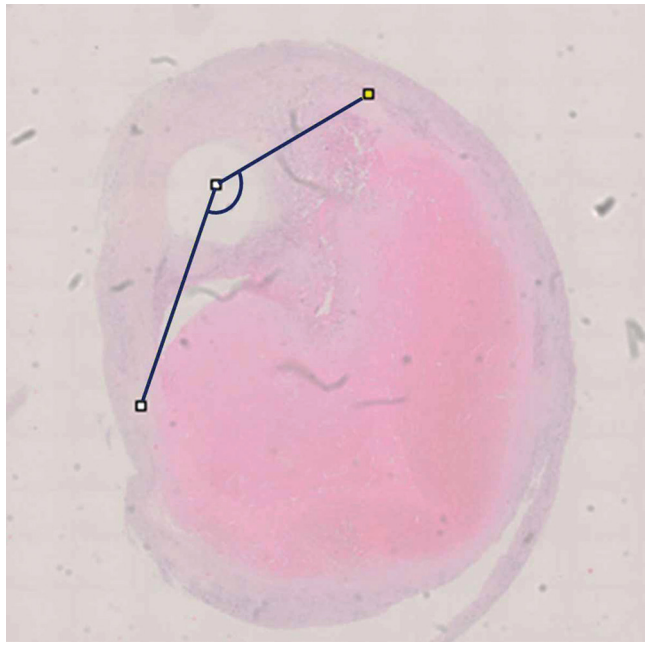

Fig. 2 The angle of lipid distribution was measured from the center of the lumen.

Data and statistical analysis

All statistical analyses were performed with SPSS version 20.0 (IBM Corp., Armonk, NY, USA). The correlations between histological specimens and maxLCBI values were analyzed using the Spearman test.

Results

In all, 15 patients (14 men, 1 woman; age range 65–84 years [mean age 73.5 years]; 11 symptomatic cases; stenosis rate (NASCET[11] method), 50% to 95% [mean 78.8 %]) had a vessel assessed by NIRS-IVUS, resulting in 70 lesions being analyzed. Clinical characteristics of the patients included symptomatic in 11 patients, hypertension in 10 patients, and hyperlipidemia in 10. In two cases who gave up stenting due to high value of maxLCBI, *in vivo* NIRS assessment was obtained. maxLCBI values were completely consistent between *in vivo* and *ex vivo* NIRS assessment in these cases. Figure 3 shows the representative case. An 84-year-old male with symptomatic carotid artery stenosis underwent CEA. Figure 3 shows the chemogram image of NIRS in vivo (Figs. 3A–3C) and ex vivo (Figs. 3D–3F), indicating similar maxLCBI value. Figure 4 shows the histological specimens with each stain, the proportion of the lipid area.

Table 1 shows that relationship between maxLCBI and histologic findings using the Spearman test. There was a positive linear correlation between maxLCBI values and lipid angle ($r = 0.624$; $p < 0.001$) (Fig. 5A) and between maxLCBI and lipid area ($r = 0.578$; $p < 0.001$) (Fig. 5B) stained by HE. Furthermore, there was a positive linear correlation between maxLCBI values and lipid areas stained by EVG ($r = 0.534$; $p < 0.001$) (Fig. 5C). In immunohistochemical staining evaluation, the percentage areas stained for LDL, glycophorin A, CRP, and CD68 were 15.0 ± 16.0%, 10.1 ± 15.7%, 16.0 ± 22.2%, and 18.8 ± 19.0%, respectively. There was a significant positive linear correlation between maxLCBI values and lipid areas stained for CRP ($r=0.723$; $p < 0.001$) and CD68 ($r = 0.653$; $p < 0.001$). There was no significant correlation between maxLCBI and lipid areas stained for LDL and glycophorin A.

Discussion

It has been reported that lipid-rich carotid plaques are prone to ischemic complications after CAS.[2,12]. Currently, plaque imaging with MRI is commonly performed for preoperative carotid plaque diagnosis; however, accurate evaluation of lipid components of carotid plaques has not been established. In the present study, we evaluated the lipid distribution

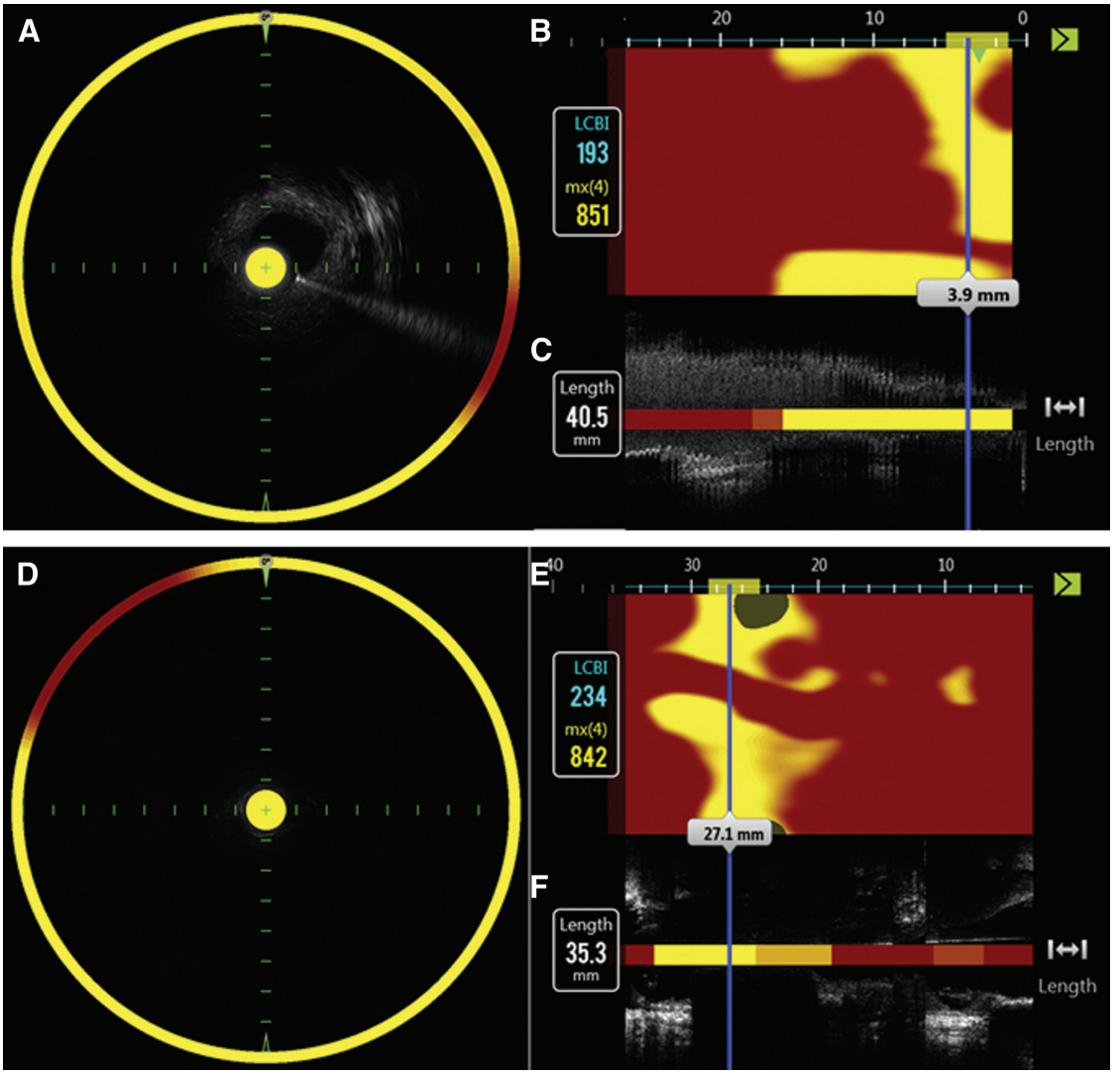

Fig. 3 Representative case of carotid artery stenosis assessed by NIRS scan and histological specimens. A and D indicate fusion image of blood vessel short-axis cross-sectional image and NIRS information by Grayscale-IVUS. B and E indicate chemogram displayed color-coded blocks according to the probability of finding a lipid plaque, if the percentage probability value for lipids was ≥ 0.98. C and F indicate long-axis cross-sectional image of blood vessel and block chemogram by Grayscale-IVUS. mx(4) indicates maxLCBI defined as the maximum value of the LCBI for 4 mm segment of blue bar. Chemogram images of NIRS in vivo (A–C; upper) and ex vivo (D–F; lower), indicating similar maxLCBI value before and after CAE. CAE: carotid endoarterectomy, IVUS: intravascular ultrasound, maxLCBI: maximum lipid core burden index, NIRS: Near-infrared spectroscopy.

of carotid plaques using NIRS-IVUS and the pathological lipid distribution using carotid intima pathological specimens harvested by CEA. We found that the carotid LCP expressed as maxLCBI values was consistent with the pathological evaluations.

In conventional carotid plaque evaluation, several previous studies have compared findings from MR plaque imaging with those from histological evaluation. Advancements in MRI plaque imaging have made it possible to identify high-risk carotid plaques[13]. Quantitative analysis of high-contrast T1-weighted images can accurately evaluate the composition of carotid plaques according to recent studies.[4,14] Previous pathological studies have shown that high intensity lesions on time-of-flight magnetic resonance angiography (MRA) are indicative of IPHs.[15,16] IPHs show higher signal intensities than LCP in MR plaque imaging; however, it can be difficult to distinguish LCP distribution where LCP is mixed with IPHs because MR signal intensity of LCP can affect IPHs.[3,5,17]

NIRS is an imaging technology that can specifically distinguish lipids and has the potential to

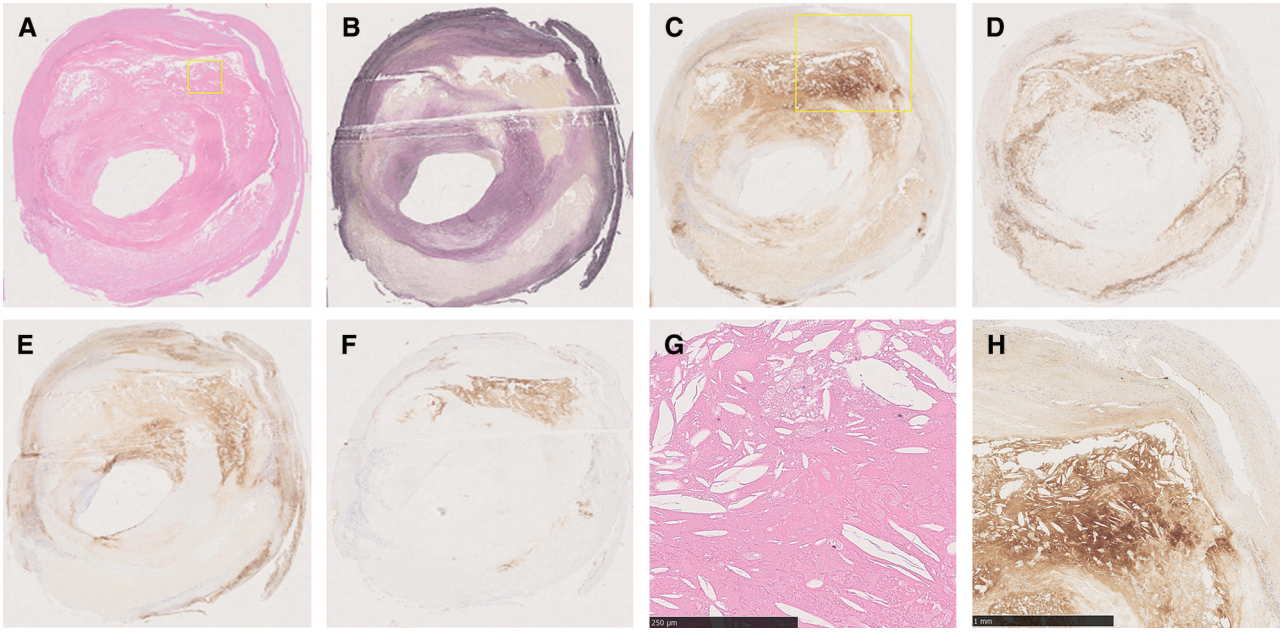

Fig. 4 Example of pathological evaluation. Histological specimens with each staining HE (A), EVG (B), CRP (C), CD 68 (D), LDL (E), and glycophorin A (F). Boxed higher magnification images of HE (G) and CRP (H) show the plaque mainly consist of lipid on microscopic specimens. CRP: C-reactive protein, EVG: Elastica van Gieson, HE: hematoxylin–eosin, LDL: low-density lipoprotein.

Table 1 Correlation between maxLCBI and histologic findings

		angle (°)	HE (area%)	EVG (area%)	LDL (area%)	CRP (area%)	CD68 (area%)	Glycophorin A (area%)
maxLCBI	Correlation coefficient	0.624	0.578	0.534	0.291	0.723	0.653	0.170
	p Value	<0.001	<0.001	<0.001	0.015	<0.001	<0.001	0.328

CRP: C-reactive protein, EVG: Elastica van Gieson, HE: hematoxylin—eosin, LDL: low-density lipoprotein, maxLCBI: maximum lipid core burden index.

compensate for the shortcomings of current modalities.[18] Goldstein et al. revealed that coronary artery lesions with maxLCBI ≥500 are associated with periprocedural myocardial infarction.[8] LCP evaluation using NIRS has become a modality to predict outcomes of coronary treatments.[19,20]. As clinical applications of NIRS for coronary artery diseases, NIRS provides accurate segments with high lipid burden and can select optimal length of the stent. Furthermore, high LCP lesion detected by NIRS can apply filter-type distal embolic protection device during stent deployment avoiding periprocedural myocardial infarction.[21] Research for plaque stabilization and reduced complications by stenting and drug therapy for unstable plaques to improve treatment is ongoing.[8,22]

Although the accuracy of lipid plaque evaluation with NIRS has been suggested for coronary arteries,[8,22,23] there are few reports on the clinical application of carotid artery lesions and therefore no reports on its consistency with histopathological evaluation.[24–26] The present study demonstrated a linear correlation between maxLCBI values and pathological evaluations of carotid plaques. We analyzed both the lipid core angle and area in pathological evaluations because the maxLCBI values as measured by NIRS indicate not the area, but the angle of the lipid plaque distribution. Consequently, both the pathological lipid area and angle were correlated with maxLCBI values in this study, which suggests that maxLCBI values indicate carotid lipid core volumes. The high value of maxLCBI which stands for a wide angle of lipid plaque distribution could be a surrogate marker that predicts PP and clinical ischemic events during CAS.

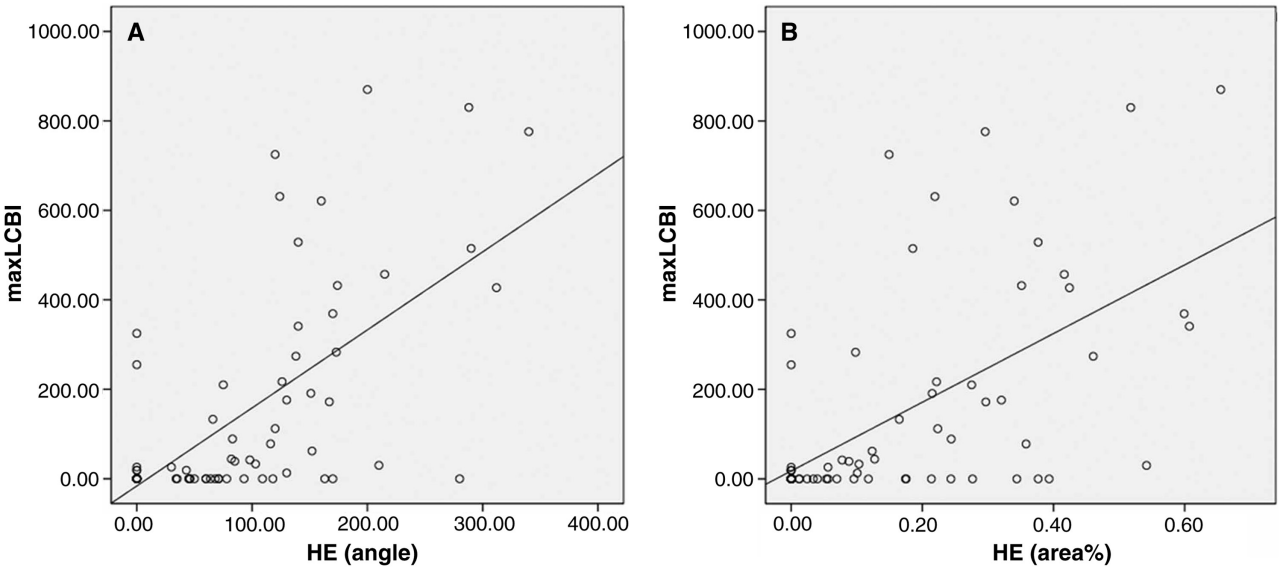

Fig. 5 Relationship between maxLCBI and histologic findings. (A) maxLCBI and angle of lipid core and (B) maxLCBI and area% stained by HE. HE: hematoxylin—eosin, maxLCBI: maximum lipid core burden index.

Immunohistochemical staining evaluation provides specific information about local inflammation. CRP and CD68 are inflammatory markers. Macrophages form by phagocytosing oxidized LDL cholesterol and remnants deposited on the blood vessel wall, and oxidized LDL, homocysteine, and CRP cause chronic inflammation [27,28]. The expression of CRP increases in advanced lesions in coronary arteries, and CRP is distributed mainly in LCPs. The expression of CRP reflects a chronic inflammatory state of the vascular wall caused by the deposition of oxidized LDL. In the present study, there was a significant correlation between maxLCBI values and CRP/CD68-positive areas. Some reports have described that the CRP-positive rate is involved in unstable plaques.[10,27] The restenosis rate is high in groups with high CRP-positive rates in histological specimens after atherectomy of coronary arteries.[27] Furthermore, CD68-expressing macrophages are localized in the lipid cores of unstable plaques without bleeding.[10] This is consistent with the present results. In contrast, oxidized LDL is considered to be a key factor in the initiation and acceleration of atherosclerosis. The association between oxidized LDL and the instability of carotid plaques has been reported.[29] Although there was no correlation between maxLCBI values and the percentage area stained by oxidized LDL in this study, the phase of atherosclerotic development including an acute or chronic stroke phase may have influenced the results. Further study will be required to clarify the association between maxLCBI values and oxidized LDL considering the atherosclerotic phase.

In the present study, we found that NIRS can accurately evaluate the distribution of LCP in carotid plaques, and this was validated by pathological consistency. Greyscale-IVUS is widely used for assessing plaque morphology, and virtual histology IVUS (VH-IVUS) has been developed to improve on the plaque characterization of greyscale-IVUS. However, previous study suggested that VH-IVUS overestimates lipid LCP in the presence of calcification, which can explain the discrepancy between VH-IVUS and NIRS findings in coronary artery study.[30] NIRS can provide an additional information to discriminate LCP at high risk for cerebral embolism during CAS. Precise assessment of LCP in carotid plaque with catheter-based NIRS could be clinically applied to embolic protection system modification including flow reversal with Mo.Ma, stent selection such as mesh-covered or double-layered stent during CAS procedure and judgment of additional medication including lipid-modification and antiplatelet therapies.[31,32] Recently, Sato et al. found that IPH rather than LCP is more likely to cause embolic complications in CEA procedures.[33] Therefore, switching CAS to CEA in patients with vulnerable plaques and high maxLCBI values may help to avoid perioperative embolic complications. Treatment selection based on the maxLCBI values as measured by NIRS could be an important diagnostic modality to improve clinical outcomes in patients who undergo CEA or CAS.

Limitations

The present study has several limitations. First, the number of cases was small. Second, maxLCBI

evaluation was performed *ex vivo* because of the invasiveness of NIRS-IVUS procedure *in vivo*. The specimens obtained by CEA are intimal plaques, not from the whole blood vessel, which could influence the maxLCBI values. Third, the main limitation of catheter-based NIRS imaging technique is its invasiveness, which precludes its utilization in asymptomatic patients. Finally, the differences in vessel diameter between coronary arteries and carotid arteries may influence the maxLCBI values as measured by NIRS. However, in all the specimens in the present study, we were able to measure the maxLCBI values. Further studies with a larger number of samples are needed.

Conclusions

maxLCBI values assessed by NIRS showed a significant positive linear correlation with pathological evaluations in carotid plaque. The maxLCBI values in carotid arteries were consistent with pathological evaluations.

Conflicts of Interest Disclosure

No declaration of sources of funding.
No statement of authorship, conflicts of interest, ethical adherence, and any financial disclosures.

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