Vasa Vasorum and Plaque Neovascularization on Contrast-Enhanced Carotid Ultrasound Imaging Correlates With Cardiovascular Disease and Past Cardiovascular Events

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Background and Purpose—Histological data associate proliferation of adventitial vasa vasorum and intraplaque neovascularization with vulnerable plaques represented by symptomatic vascular disease. In this observational study, the presence of carotid intraplaque neovascularization and adventitial vasa vasorum were correlated with the presence and occurrence of cardiovascular disease (CVD) and events (CVE).

Methods—The contrast-enhanced carotid ultrasound examinations of 147 subjects (mean age 64±11 years, 61% male) were analyzed for the presence of intraluminal plaque, plaque neovascularization (Grade 1=absent; Grade 2=present), and degree of adventitial vasa vasorum (Grade 1=absent, Grade 2=present). These observations were correlated with preexisting cardiovascular risk factors, presence of CVD, and history of CVE (myocardial infarction and transient ischemic attack/stroke).

Results—The presence of intraluminal carotid plaque was directly correlated to cardiovascular risk factors, CVD, and CVE ($P<0.05$). Adventitial vasa vasorum Grade 2 was associated with significant more subjects with CVD than vasa vasorum Grade 1 (73 versus 54%, $P=0.029$). Subjects with intraplaque neovascularization Grade 2 had significantly more often a history of CVE than subjects with intraplaque neovascularization Grade 1 (38 versus 20%, $P=0.031$). Multivariate logistic regression analysis revealed that presence of plaque was significantly associated with CVD (odds ratio 4.7, 95% CI 1.6 to 13.8) and intraplaque neovascularization grade 2 with CVE (odds ratio 4.0, 95% CI 1.3 to 12.6).

Conclusion—The presence and degree of adventitial vasa vasorum and plaque neovascularization were directly associated with CVD and CVE in a retrospective study of 147 patients undergoing contrast-enhanced carotid ultrasound. **(*Stroke*. 2010;41:00-00.)**

Key Words: neovascularization ■ vasa vasorum ■ contrast ultrasound

Hyperplasia of adventitial vasa vasorum and intraplaque neovascularization are important features in plaque development.[1–4] Recent studies confirmed a pronounced association between intraplaque neovascularization, plaque vulnerability, and cardiovascular events (CVE).[5–8] The events which lead to plaque rupture and clinical events appear to be initiated and triggered by vascular leakage, inflammatory cell recruitment, and intraplaque hemorrhage; all consistent with plaque inflammation processes.[1]

Contrast-enhanced carotid ultrasound (CECU) provides direct visualization of the adventitial vasa vasorum and intraplaque neovascularization,[9–12] using the fact that contrast agents microspheres are ideal intravascular tracers, thus permitting a noninvasive assessment of the dynamic spatial and temporal heterogeneity of the intraplaque microvasculature.[13] Recently, we and others described a positive correlation between histological density of neovessels and the presence of neovascularization in carotid plaques detected by CECU.[14,15] Though a relationship exists between plaque angiogenesis and increased plaque instability and vascular complications, the implications of detecting adventitial vasa vasorum and intraplaque neovascularization in human carotid atherosclerotic lesions assessed by CECU remains unknown.[16] Therefore, in this retrospective study, we correlated the clinical history of cardiovascular disease (CVD) and CVE with the degree of carotid artery adventitial vasa vasorum and intraplaque neovascularization.

Methods

Patient Enrollment

Between January 2004 and September 2008, 159 consecutive subjects underwent carotid duplex ultrasound examinations at Rush University Medical Center, Chicago, Ill. All subjects were referred

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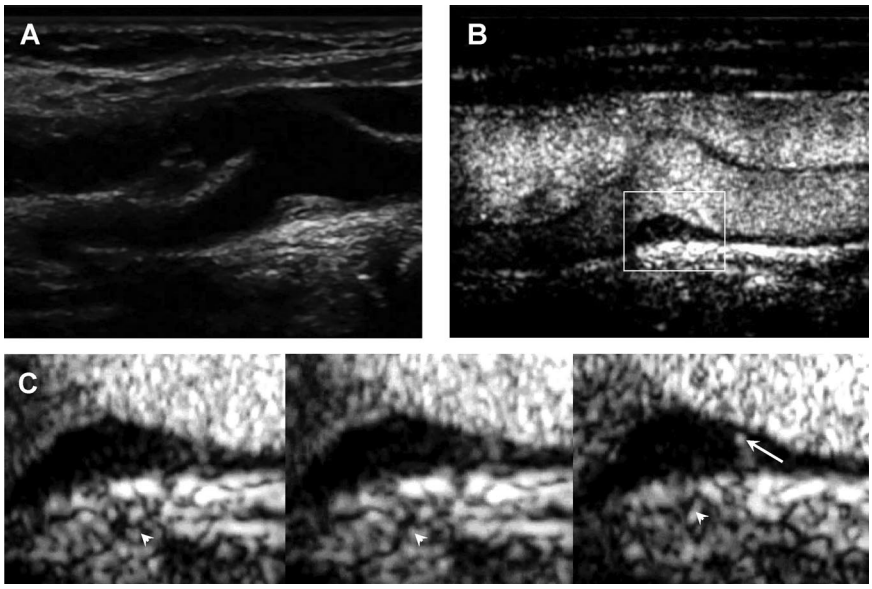

Figure 1. Carotid artery with vasa vasorum grade 2 on contrast-enhanced ultrasound. A, Plaque on B-mode ultrasound imaging at the origin of the internal carotid artery. B, Corresponding presentation on contrast-enhanced ultrasound imaging. C, Zoom of consecutive frames of this lesion with visible microbubbles in the periadventitial tissue (small arrow) and within the plaque (long arrow; also see Supplemental Video 1, available online at http://stroke.ahajournals.org).

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for carotid duplex ultrasound examination based on appropriate clinical indications. Subjects who were >18 years of age and could provide informed consent were included in this study. Exclusion criteria were known allergies to albumin, or to the ultrasound contrast agent. Once enrolled, the subjects underwent a standard carotid duplex ultrasound examination, and 93% of all examinations were followed by the contrast portion of the study. In 12 patients no ultrasound contrast agents were applied for different reasons (refusal, availability, shortage of time, etc.). Therefore, 147 patients underwent CECU and were included in the primary analysis. The clinical research study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committee (Rush University Medical Center, IRB #2, ORA# 01062001). Written informed consent was obtained from all participating patients.

Standard and Contrast-Enhanced Carotid Ultrasound Imaging

The carotid ultrasound examinations were performed using a GE VIVID 7, (GE Healthcare) or ATL HDI 5000 (Philips) ultrasound system, equipped with a 7-L or 7–4–MHz linear transducer equipped with ultrasound contrast software. The examination of both left and right carotid arteries consisted of B-mode ultrasound imaging, color Doppler ultrasound, and pulsed Doppler spectral analysis of the common carotid artery, the extracranial segments of the internal carotid artery, and the external carotid artery. On completion of the noncontrast portion of the examination, ultrasound contrast agents were infused according to protocol as previously described.[14]

For each machine the following setting for ultrasound contrast were implemented. ATL HDI 5000 system: 7–4–MHz linear array vascular probe with General Imaging harmonic software, mechanical index 0.06 to 0.1; GE VIVID 7 system: 7L probe with harmonic software, mechanical index 0.18 to 0.20. The overall gain, time gain compensation and compression were optimized and provided as "pre sets."

All CECU studies were performed using perflutren protein type-A microspheres (Optison, GE Healthcare) or perflutren lipid microspheres (Definity, Bristol-Myers Squibb Medical Imaging) ultra-

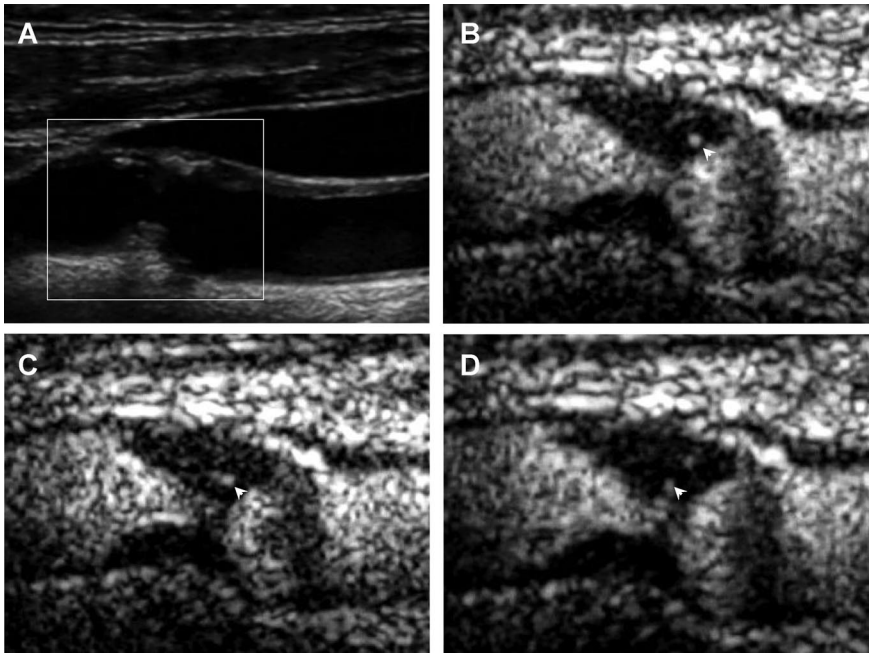

Figure 2. Carotid artery with intraplaque neovascularization grade 2 on contrast-enhanced ultrasound. A, Plaque at the origin of the internal carotid artery. Corresponding consecutive frames on contrast enhanced ultrasound (B and C) with visible microbubbles within the plaque (arrow; also see Supplemental Video 2, available online at http://stroke.ahajournals.org).

sound contrast agents. The ultrasound contrast agent Optison and Definity, supplied as 3-mL and 1.5-mL vials, were diluted with 7 mL and 8.5 mL of 0.9% saline, respectively, resulting in a total of 10 mL of infusate. The contrast agent was injected via a peripheral vein as a bolus of 2 mL followed by a saline bolus of 2 to 3 mL and further injection as required. The standard and CECU studies were recorded on VHS videotape or stored digitally for offline further analysis and quantification by the main investigator (D.S.) who remained blinded to the patient demographics.

Based on standard ultrasound images, the presence of atherosclerotic plaques was considered according to the Mannheim consensus as focal structures encroaching into the arterial lumen.[17] Stenoses were graded according to current guidelines.[18]

After the injection of ultrasound contrast agents, the lumen of carotid artery was enhanced within 10 to 30 seconds. Using a low mechanical index setting and the contrast-enhanced harmonic software, carotid plaques and the intima-media complex appeared hypoechoic with the adventitial layer bright echogenic. The presence of blood flow "activity" within the adventitial layer or the plaque was identified based on the dynamic movement of the echogenic reflectors (microspheres) observed within the adventitial vasa vasorum and intraplaque microvessels, whereas, fixed echogenic reflectors were considered as strong acoustic reflections based on tissue reflectivity.

Adventitial vasa vasorum activity was graded based on the presence of visible microspheres confined to the adventitial layer or the adjacent 5 mm of the periadventitial tissue located along the far wall of the common carotid artery or bifurcation: Grade 1: no microspheres noted in the adventitial layer and adjacent periadventital tissue; grade 2: clear visible microspheres within the adventitial layer or adjacent periadventitial tissue (Figure 1). Intraplaque neovascularization (contrast-agent enhancement) was categorized using a modified grading scale published previously[14]: grade 1 was used to indicate no appearance of bubbles within the plaque or bubbles confined to plaque adventitial side. Grade 2 reveals a clear visible appearance of bubbles within the plaque moving from the adventitial side or shoulder reaching plaque core (Figure 2). The highest grade of vasa vasorum and intraplaque neovascularization (right or left side) along with the corresponding plaque thickness and stenosis severity were used for the analyses.

F1 F2

Patient's Baseline Characteristics

Three coauthors (M.B.P., A.T., D.L.) who were blinded to the results of the CECU performed a review of the clinical charts and included the following: cardiovascular risk factors (hypertension, diabetes mellitus, smoker, lipids), history of myocardial infarction (MI), coronary or peripheral vascular revascularization, previous stroke or transient ischemic attack (TIA), and medications (contemporaneous with the carotid duplex ultrasound examination). Stroke and TIA were confirmed from hospital discharge reports or from documented neurological evaluations. MI was defined as a positive troponin T/I or at least 2-fold increase of creatinine kinase-MB with ST-elevation or with other typical ECG alterations without ST-elevation.

The following definitions were used for cardiovascular risk factors: hypertension (blood pressure $\geq$140/$\geq$90 mm Hg or antihypertensive drug), confirmed diabetes mellitus type 1 or 2 or medication for diabetes, and current or former smoker. Included in the definition of a history of CVD were the following: peripheral arterial occlusive disease (ankle-arm index $<$0.9 or previous intervention on the leg vessels), coronary artery disease confirmed by stress test or coronary angiography, history of MI, or cerebrovascular disease including history of TIA or stroke. Included in the definition of a history of CVE was the history of MI, TIA, or stroke.

Statistical Analysis

Statistical analysis was performed using SPSS/PC (version 12.0, SPSS Inc). Comparisons between baseline characteristics, the presence of plaque, degree of vasa vasorum, and intraplaque neovascularization were made using analysis of variance (ANOVA) for independent samples or χ^2 tests as appropriate. Multivariate logistic regression analyses were performed for CVD and CVE including all factors found to be significant on univariate logistic regression analyses (age, diabetes mellitus, hypertension, low-density lipoprotein, statin, presence of plaque, vasa vasorum grade 2, intraplaque neovascularization grade 2). For determination of intraobserver and interobserver variability, Cohen kappa was used to measure agreement between two different readers and between two different assessments of one reader using the established grading of agreement[19]: $<$0 (no agreement), 0 to 0.2 (poor), 0.21 to 0.4 (fair), 0.41 to 06 (moderate), 0.61 to 0.8 (substantial), and 0.81 to 1.0 (nearly perfect).

Table 1. Baseline Characteristics of All Consecutive Patients (n=147) Undergoing Contrast-Enhanced Carotid Ultrasound Imaging

Cardiovascular risk factors	
Age, y	64±11
Male gender	89 (61)
BMI, kg/m^2	29±7
Diabetes mellitus	45 (31)
Hypertension	100 (68)
Current or former smoker	68 (46)
Lipids, mg/dL	
LDL	87±43
HDL	53±16
Total cholesterol	164±50
Triglycerides	122±70
Use of drugs	
Antihypertensive medication	114 (78)
Statins	127 (86)
Diabetes medication	41 (28)
Antipletelet drugs or oral anticoagulation	121 (82)
Clinical history	
Coronary artery disease	77 (52)
Myocardial infarction	22 (15)
TIA/stroke	17 (12)
Peripheral artery disease	23 (16)
Cardiovascular disease	89 (61)
Cardiovascular events	37 (25)

Data are expressed as mean±SD or No. (percentage) of subjects.

BMI indicates body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TIA, transient ischemic attack.

Results

Patient's Characteristics

The characteristics of the study population referred for CECU are listed in Table 1. Among the 147 subjects, 83% had more than one cardiovascular risk factor. Established CVD was documented in 61% of all subjects. Previous MI occurred in 22 (15%) and TIA or stroke in 17 (12%) subjects. At least one previous CVE was documented in 37 (25%) subjects. Only 6 patients had an acute cardiovascular event within 3 months before the examination date.

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Standard and Contrast-Enhanced Carotid Ultrasound Imaging

Standard ultrasound and CECU imaging revealed 1 or multiple carotid plaque(s) in 111 subjects (76%) (Table 2). A stenosis $\geq$70% was documented in 6 lesions.

T2

Table 2. Intraluminal Plaque, Adventitial Vasa Vasorum, and Intraplaque Neovasularization on Contrast-Enhanced Carotid Ultrasound Imaging and Association With Clinical Characteristics

	Intraluminal Plaque		Adventitial Vasa Vasorum		Intraplaque Neovascularization	
	No (n=36)	Yes (n=111)	Grade 1 (n=99)	Grade 2 (n=48)	Grade 1 (n=51)	Grade 2 (n=60)
Cardiovascular risk factors						
Age, y	58±12	66±10*	64±11	66±12	66±10	66±10
Male gender	20 (56)	69 (62)	57 (58)	32 (67)	34 (67)	35 (58)
Diabetes mellitus	4 (11)	41 (37)†	28 (28)	16 (33)	22 (43)	18 (30)
Hypertension	14 (39)	86 (77)*	64 (65)	35 (73)	39 (76)	45 (75)
Current or former smoker	11 (31)	57 (51)	47 (47)	21 (44)	27 (54)	30 (50)
Lipids, mg/dL						
LDL	106±60	83±34†	86±32	92±59	78±28	87±38
HDL	52±18	53±16	52±16	55±16	50±12	56±19
Total cholesterol	180±73	160±40†	160±40	172±65	151±33	166±44
Triglycerides	115±58	124±73	123±71	122±68	128±84	123±62
Statins	28 (78)	99 (89)	84 (85)	42 (87)	44 (86)	53 (88)
Clinical history						
Coronary artery disease	7 (19)	70 (63)*	46 (46)	30 (63)	30 (59)	38 (63)
Myocardial infarction	1 (3)	21 (19)†	10 (10)	12 (25)†	4 (8)	17 (28)†
TIA/stroke	2 (6)	15 (14)	11 (11)	6 (13)	6 (12)	8 (13)
Peripheral artery disease	0 (0)	23 (21)†	13 (13)	10 (21)	7 (14)	15 (25)
Cardiovascular disease	8 (22)	81 (73)*	53 (54)	35 (73)†	33 (65)	46 (77)
Cardiovascular events	3 (8)	34 (31)†	20 (20)	17 (35)	10 (20)	23 (38)†
Ultrasound findings						
Presence of plaque(s)	0 (0)	111 (100)	69 (70)	43 (90)†	53 (100)	60 (100)
Stenosis <50%	NA	87 (78)	54 (78)	34 (79)	44 (82)	45 (75)
Stenosis 50–69%	NA	18 (16)	13 (19)	5 (28)	7 (14)	11 (18)
Stenosis ≥70%	NA	6 (6)	2 (3)	4 (9)	2 (4)	4 (7)
Max plaque thickness, mm	NA	2.82±0.82	2.77±0.80	2.90±0.86	2.77±0.88	2.86±0.77

Data are expressed as mean±SD or No. (percentage) of subjects. Analysis of variance (ANOVA) or χ^2-test compared with no plaque, vasa vasorum grade 1, and Intraplaque neovascularization grade 1, respectively: *$P<0.001$; †$P<0.05$.

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; TIA, ransient ischemic attack; NA, not applicable.

Among the 111 subjects with intraluminal plaques, no intraplaque neovascularization (grade 1) was found in 51 subjects and intraplaque enhancement with documented microsphere activity (intraplaque neovascularization grade 2) was noted in 60 subjects (54%). Further, a total of 8 carotid plaque ulcerations were newly detected following CECU. Vasa vasorum grade 1 was documented in 99 subjects, and an increased enhancement with visible microspheres within the adventitial layer or adjacent periadventitial tissue (vasa vasorum grade 2) was noted in 48 subjects (33%).

Factors Associated With the Presence of Plaque, Intraplaque Neovascularization, and Vasa Vasorum

As shown in Table 2, the presence of plaque was significantly associated with older age, diabetes mellitus, hypertension, lower level of low-density lipoprotein, and total cholesterol. Subjects with documented carotid plaques were more likely to have established CVD and documented history of CVE than subjects without plaques, 73% versus 22% ($P<0.001$) and 31% versus 8% ($P=0.012$), respectively (Figure 3). F3

In subjects with carotid plaques, the degree of vasa vasorum on contrast-enhanced ultrasound imaging was more pronounced than in those individuals without identifiable plaques. Adventitial vasa vasorum grade 2 was found in 38% of subjects with plaques as compared to 15% in subjects without plaques ($P=0.01$).

Higher grade of vasa vasorum on CECU imaging was not associated with cardiovascular risk factors (Table 2). However, subjects with pronounced vasa vasorum (grade 2) were more likely to exhibit established CVD than those subjects with no vasa vasorum (grade 1), 73% versus 54% ($P=0.032$; Figure 3). Although subjects with higher grade of vasa vasorum (grade 2) exhibited a history of MI more often than subjects with no vasa vasorum (grade 1), 25% versus 10% ($P=0.026$); the prevalence of CVE between these 2 groups was not statistically significant, 35% versus 20% ($P=0.068$).

The presence of intraplaque neovascularization grade 2 on CECU imaging among subjects with documented plaques was not associated with any cardiovascular risk factors (Table 2). The prevalence of CVD was similar in subjects with

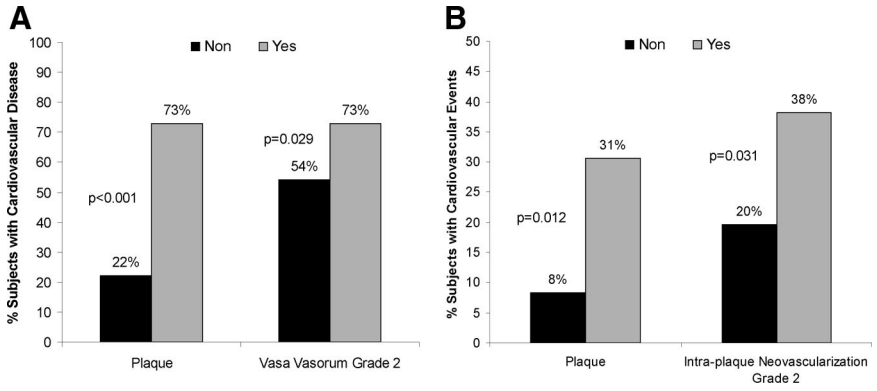

Figure 3. Plaque, vasa vasorum, and intraplaque neovascularization in subjects with cardiovascular disease and history of cardiovascular events. A, Percentage of subjects with history of cardiovascular disease in subjects without (black bar) and with (gray bar) plaque and vasa vasorum grade 2. B, Percentage of subjects with history of cardiovascular events in subjects without (black bar) and with (gray bar) plaque and intraplaque neovascularization grade 2.

intraplaque neovascularization grade 1 and grade 2, 65% versus 77% ($P=0.208$). However, subjects with intraplaque neovascularization grade 2 had a higher incidence of a prior CVE as compared to subjects without intraplaque neovacularization, 38% versus 20% ($P=0.031$).

Univariate and Multivariate Analysis for Patients With Cardiovascular Disease and Events

As shown in Table 3, univariate logistic regression analysis of cardiovascular risk factors and carotid ultrasound data showed that older age, diabetes mellitus, and hypertension, as well as the presence of plaque, were all significantly associated with CVD and history of CVE ($P<0.05$). Vasa vasorum grade 2 was significantly associated with CVD (odds ratio 2.3, $P=0.031$) and intraplaque neovascularization grade 2 was significantly associated with CVE (odds ratio 2.5, $P=0.034$).

Multivariate logistic regression analysis including all factors found to be significant on univariate analysis revealed that the presence of plaque was the most significant and independent finding associated with CVD (odds ratio 4.7, $P=0.005$), and the presence of intraplaque neovascularization was the most significant and independent marker associated with a history of CVE (odds ratio 4.0, $P=0.017$).

Reproducibility of Contrast-Enhanced Carotid Ultrasound Findings

To establish the reproducibility of our qualitative assessment, intraobserver and interobserver agreement applying Cohen kappa[19] was determined by grading 100 carotid arteries for intraluminal plaque, intraplaque neovascularization, and vasa vasorum by 2 different readers and by 1 reader at an interval of more than 7 days using video loops of CECU. Nearly perfect intraobserver agreement (kappa coefficient 0.82) and

Table 3. Univariate and Multivariate Analysis for Patients With History of Cardiovascular Disease and Events

	Cardiovascular Disease		Cardiovascular Events	
	Odds Ratio (95%CI)	*P* Value	Odds Ratio (95%CI)	*P* Value
Univariate analysis				
Age, y	1.09 (1.04–1.13)	<0.001	1.06 (1.02–1.10)	0.004
Diabetes mellitus	4.5 (1.9–10.5)	<0.001	2.5 (1.1–5.4)	0.021
Hypertension	4.5 (2.2–9.5)	<0.001	2.4 (1.0–6.1)	0.054
Current or former smoker	1.3 (0.7–2.5)	NS	1.3 (0.6–2.7)	NS
LDL, mg/dL	0.99 (0.97–1.00)	0.007	1.00 (0.99–1.01)	NS
Statins	6.4 (2.4–17.2)	<0.001	3.0 (0.8–10.5)	NS
Presence of plaque	8.3 (3.4–20.1)	<0.001	4.5 (1.3–15.5)	0.019
Vasa vasorum grade 2	2.3 (1.1–4.8)	0.031	2.1 (1.0–4.6)	0.053
Intraplaque neovascularization grade 2	1.8 (0.8–4.1)	NS	2.5 (1.1–6.1)	0.034
Multivariate analysis				
Age, y	1.05 (1.00–1.10)	0.046	1.04 (0.99–1.09)	NS
Diabetes mellitus	2.1 (0.8–5.7)	NS	2.1 (0.9–5.2)	NS
Hypertension	2.5 (1.0–6.3)	0.052	1.8 (0.6–5.4)	NS
LDL, mg/dL	1.00 (0.99–1.01)	NS	1.01 (0.99–1.02)	NS
Statins	4.8 (1.2–19.4)	0.026	3.7 (0.6–22.5)	NS
Presence of plaque	4.7 (1.6–13.8)	0.005	2.1 (0.5–8.9)	NS
Vasa vasorum grade 2	1.7 (0.7–4.3)	NS	1.7 (0.7–4.1)	NS
Intraplaque neovascularization grade 2	2.0 (0.7–5.9)	NS	4.0 (1.3–12.6)	0.017

CI indicates confidence interval; NS, not significant; LDL, low-density lipoprotein.

substantial interobserver agreement (kappa coefficient 0.77) on the presence or absence of intraluminal plaque was found. Intraobserver agreement on the presence or absence of intraplaque neovascularization was substantial (kappa coefficient 0.63) and on the presence or absence of vasa vasorum was moderate (kappa coefficient 0.51). Moderate interobserver agreement on the presence or absence of intraplaque neovascularization (kappa coefficient 0.54) and vasa vasorum (kappa coefficient 0.44) was documented.

Discussion

In the present study we confirmed the hypothesis that adventitial vasa vasorum and intraplaque neovascularization identified using CECU imaging are associated with CVD and CVE. To our knowledge, this is the first large study in which CECU findings of vasa vasorum and intraplaque neovascularization were correlated to subjects' clinical history. This study also highlights the potential uses of noninvasive imaging for the detection of new surrogate markers of atherosclerosis.

The use of ultrasound contrast agents for the detection of vasa vasorum as an indicator of premature atherosclerosis has garnered considerable interest when used to identify and quantify carotid artery adventitial vasa vasourm and neovascularization of the atherosclerotic plaque.[9–12] Histopathological validation studies revealed a positive direct correlation between contrast enhancement and quantitative histology.[14,15]

In the present study, we found in accordance with previous studies a close relationship between the presence of plaque and cardiovascular risk factors, CVD, and CVE.[20–22] Moreover, in our study, we focused on adventitial vasa vasorum and intraplaque neovascularization, which comprise 2 distinct microvascular networks that are inescapably linked to the evolution of symptomatic occlusive atherosclerotic disease.[1] Notably, increased degree of vasa vasorum was associated with established CVD, and in patients with documented plaques a direct correlation between intraplaque neovascularization and a history of CVE was observed. It is noteworthy that these findings are consonant with concepts as described by Fleiner et al, in which the authors posited that arterial neovascularization as hyperplasia of vasa vasorum and ectopic intraplaque neovascularization are harbingers of symptomatic pan-arterial atherosclerosis.[5] Furthermore, analyses of unstable carotid lesions demonstrated that the presence of intraplaque hemorrhage and microvessel density were directly associated with plaque rupture.[6,7] Dunmore et al reported that symptomatic atherosclerotic carotid plaques were associated with abnormal and immature intraplaque microvessels and noted that such vessels could contribute to plaque friability by promoting vascular leakage and deposition of inflammatory cell recruitment within the plaque.[8]

Several studies support the concept that changes found in unstable plaques are not merely a local vascular incident but rather represent uniformly distributed inflammation markers throughout the systemic vascular bed.[5,23] In one study using MRI, Lombardo et al[24] found that 89% of carotid plaques enhanced with gadolinium indicating increased neovascularization in patients with acute coronary syndromes, whereas only 8% revealed similar enhancement in the control group. Thus, consistent with the published data, our results indicated that the associated risk for a cerebrovascular event assessed from carotid plaque characteristics applies also to other systemic vessels including coronary events.[25] These findings, based on credible evidence, support the concept that increased intraplaque neovascularization is emblematic of an inflamed arterial vessel associated with plaque instability, and consequently identifying an "at risk" patient.

Study Limitations

Several limitations should be considered in interpreting our results. First, as associated with retrospective analyses in selected subjects referred for clinical indications, our results require prospective confirmation in a larger unselected study population. Second, we used a semiquantitative visual approach which has been previously published to evaluate and quantify contrast enhancement of the adventitial vasa vasorum and intraplaque neovascularization.[14,15] In future applications, it is anticipated that the use of computer-assisted quantitative analyses of intraplaque neovasculature will provide additional value. Third, our population consisted of subjects with a predominance of cardiovascular risk factors and expressed CVD (76% exhibited carotid lesions), therefore our focus was directed at assessing carotid plaque neovascularization not measurements of carotid intima-media thickness. Though, previously, Magnoni et al[12] reported on the direct association between adventitial vasa vasorum and carotid intima-media thickness. This combined approach may be valuable in future prospective studies, which includes screening of subjects considered to be at lower risk.

Conclusion

Pronounced enhancement of adventitial vasa vasorum on CECU was associated with established CVD, and the presence of vasa vasorum–derived intraplaque neovascularization was associated with a history of CVE (MI, TIA, and stroke), supporting the concept that intraplaque neovascularization is associated with plaque instability and vulnerability. Therefore, the use of CECU imaging may provide a noninvasive adjunctive "window" to risk stratify individuals by identifying "vulnerable" plaques and may serve as a valuable screening tool to identify patients at high risk of CVE.

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Disclosures

None. **AQ: 3**

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