Sonographic Carotid Plaque Morphologic Characteristics and Vascular Risk Factors

Results From a Population Study

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Objective. The role of vascular risk factors in atherosclerosis development is well established, whereas risk factors involved in determining plaque vulnerability are still a matter of debate. We investigated the vascular risk factor distribution in patients with carotid plaques. ***Methods.*** We consecutively assessed sonographic plaque morphologic characteristics, the degree of stenosis, and the common carotid artery intima-media thickness (IMT) in 1655 patients. Demographic data, a documented history of symptomatic cerebrovascular disease (CVD), and the presence of vascular risk factors were collected. According to literature, heterogeneous hypoechoic plaques with an irregular surface or ulcerations and those with a severe degree of stenosis (≥70%) have been considered "complex" plaques at "major" risk of stroke; homogeneous hyperechoic plaques with smooth surface lesions have been considered "simple" plaques at minor risk. ***Results.*** Univariate analysis showed that all vascular risk factors were associated with the presence of carotid atherosclerotic lesions. Multiple logistic regression showed an independent association of hypertension and diabetes with complex plaques, which also had a thicker IMT. A history of CVD was observed more frequently in complex plaques, which had a higher stenosis percentage even after patients with a severe degree of stenosis (≥70%) and indications for carotid surgery were excluded. ***Conclusions.*** Hypertension and diabetes are related to a thicker IMT and more severe complex plaques, which may reflect the instability of atherosclerotic process. Because two-thirds of the patients with complex plaques were asymptomatic for CVD, this raises the importance of surveillance sonography to monitor plaque evolution for prevention of symptomatic CVD. ***Key words:*** carotid atherosclerosis; sonography; stroke prevention; unstable plaques; vascular risk factors.

Abbreviations
CVD, cerebrovascular disease; GSM, gray scale median; IMT, intima-media thickness

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Morphologic studies with sonography have identified echographic plaque characteristics that may reflect higher plaque vulnerability, ie, the likelihood of developing cerebral embolisms through local thrombus formation and surface ulcerations. Heterogeneous plaques with low echogenicity that are composed of atheromatous material, cholesterol and lipid deposits, and areas of intraplaque hemorrhage are at high risk of possible rupture of the surface endothelium with subsequent ulcerations, distal embolization, and stroke.[1–3] Objective quantification of

echogenicity through computerized analysis (gray scale median [GSM]) has also proved a reliable tool for identifying hypoechoic plaques at major risk of evolution and development of future cerebrovascular events.[4,5] Therefore, the definition of an "unstable plaque"[6] and the concept of the severity of stenosis are no longer the only standards for evaluation when considering patients as candidates for surgery.[7,8]

As an index of lesion vulnerability,[9] the inflammatory process has brought about the development of new imaging techniques aimed at evaluating the biological "functional" status of an atherosclerotic lesion, namely the "plaque activity." New advances in conventional radiologic imaging such as computed tomographic angiography, magnetic resonance angiography, and fluorodeoxyglucose F 18 positron emission tomography have focused on the evaluation of the plaque activity, but to date, there has been no overall consensus as to which type of imaging is the reference standard.[10,11] With the development of software for B-mode image analysis[4,5,12] and new functional contrast agent technologies, carotid sonography is able to provide valuable data on other features in addition to echographic morphologic characteristics, such as plaque motion[6,8,13] and the presence of intraplaque angiogenesis,[14,15] which is responsible for plaque inflammation and thus a heterogeneous hypoechoic structure with greater vulnerability.

Although the role of classic vascular risk factors in atherosclerosis is well established, risk factors involved in determining plaque vulnerability are still objects of research. Actual studies have focused on the role of inflammation and inflammatory markers, but few have reported a direct correlation between plaque vulnerability and cardiovascular risk factors. Several authors[16–18] reported that hypoechoic carotid artery plaques were associated with elevated lipid plasma levels and with low high-density lipoprotein and postprandial triglyceride-rich lipoprotein levels. Furthermore, patients with type 2 diabetes have more hypoechoic plaques compared with nondiabetic patients and thus are at higher risk of cardiovascular events.[19]

The aim of our study was to investigate the clinical features and vascular risk factor distribution in patients with carotid plaques evaluated by sonography and to analyze the vascular risk factor distribution in carotid lesions with different morphologic characteristics.

Materials and Methods

Study Procedures

We designed a cross-sectional prospective open study including consecutive patients, both inpatients and outpatients, referred to the Neurosonology Laboratory of the Department of Neurological Sciences for both vascular screening and a specific neurovascular workup. The study procedures involved the usual patient protocols used for diagnostics in our laboratory.

Demographic features (age and sex), the diagnosis and documented history of symptomatic cerebrovascular disease (CVD), and the presence of vascular risk factors were collected. Hypertension was considered systolic blood pressure higher than 140 mm Hg, diastolic blood pressure higher than 90 mm Hg, or current treatment with antihypertensive drugs; smokers were considered patients who had ever had a smoking habit, current or past, and were referred to as "smoking"; diabetes was considered glycemia higher than 110 mg/dL; dyslipidemia was considered cholesterolemia higher than 240 mg/dL, trygliceridemia higher than 160 mg/dL, or current treatment with statins; and alcohol use was classified as yes or no.

Color duplex sonographic scanning was performed with an Acuson 128XP apparatus and a 5-MHz linear array transducer (Siemens Medical Solutions, Mountain View, CA). Standard presets, with a dynamic range of 60 dB and without an image postprocessing curve, were maintained constant throughout the study for all patients investigated. Plaque images were documented in the B-mode, color mode, and color mode with a pulsed wave spectrum, reporting peak systolic velocity and end-diastolic velocity and plaque areas on longitudinal and transverse scans at the point of maximum stenosis for offline analysis and quantification.

The presence of atherosclerotic plaques was considered according to the Mannheim consensus[20] as focal structures that encroached into the arterial lumen of at least 0.5 mm or 50% of the surrounding intima-media complex or that had a

thickness of greater than 1.5 mm as measured from the media-adventitia interface to the intima-lumen surface. The intima-media thickness (IMT) was measured online on frozen magnified images with the calipers of the ultrasound machine on both common carotid arteries 10 mm below the bifurcation, measuring the maximum distance between the leading edge of the luminal echo to the leading edge of the media-adventitia echo on the "far wall."[20]

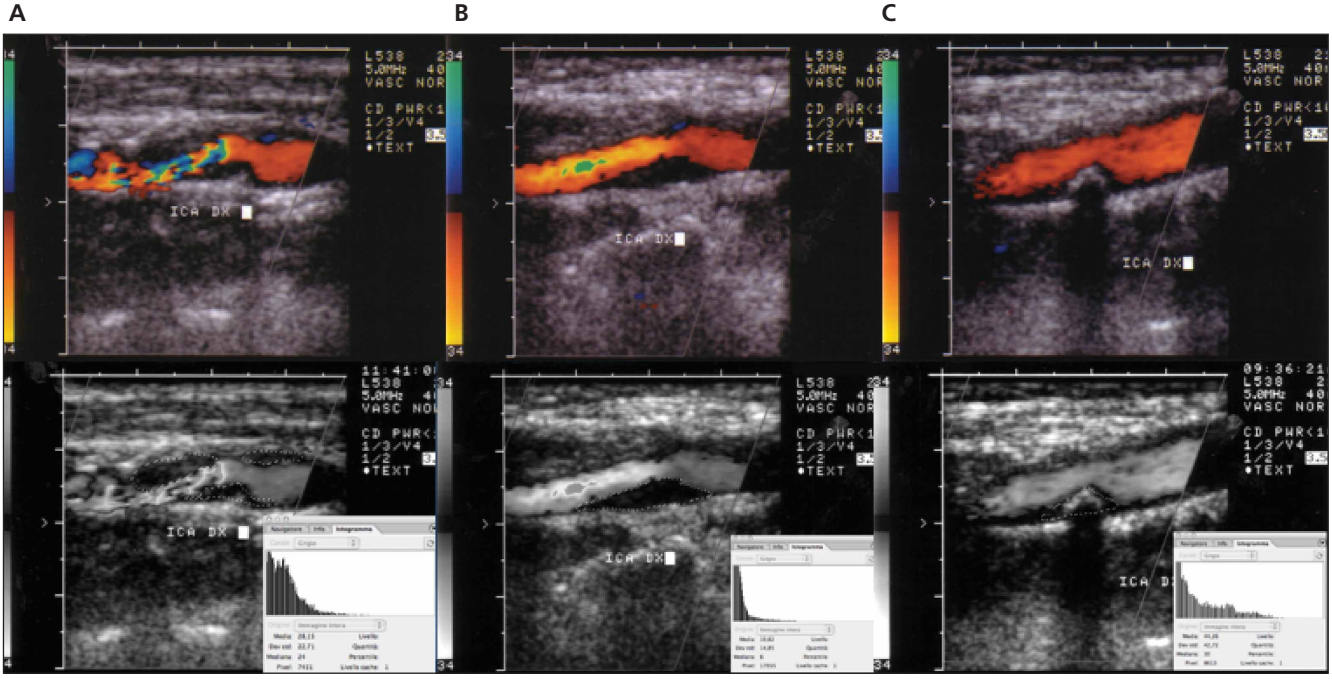
Plaque echographic morphologic characteristics were described according to criteria already well established in literature.[21,22] The plaque structure was classified by echogenicity and considered hyperechoic with an acoustic shadow, hyperechoic, isoechoic, or hypoechoic and consequently calcific, fibrous, fibrocalcific, fibrofatty, hemorrhagic, or necrotic. The plaque surface was classified as regular or irregular and ulcerated when a surface irregularity of greater than 2 mm was observed. The degree of stenosis was evaluated according to European Carotid Surgery Trial criteria[23] as the percentage of the difference between the original vessel lumen diameter/area and the residual lumen diameter/area at the maximum site of stenosis and according to the blood flow velocities.[1,24] The GSM was obtained from digitized images as described elsewhere.[4]

According to the literature,[1–6] heterogeneous hypoechoic plaques with zones of varying echogenicity, low GSM scores (<25), and surface irregularities or ulcerations and those with a severe degree of stenosis (≥70%) have been considered "complex" plaques at major risk of stroke (Figure 1, A and B). On the other hand, homogeneous hyperechoic plaques with a smooth border have been considered "simple" plaques at minor risk (Figure 1C). Consequently, we divided the patients into 2 groups: (1) patients with at least 1 complex plaque and (2) patients with only simple plaques.

Statistical Analysis

Analysis of variance and χ^2 univariate analysis were first applied to determine the association of

Figure 1. Duplex carotid sonograms of complex plaques at major risk of stroke and simple plaques at minor risk. **A**, Top, Complex heterogeneous isoechoic to hypoechoic plaque with a distal anechoic part and an irregular surface, indicating severe internal carotid artery stenosis. Bottom, Low GSM on computerized analysis. **B**, Top, Complex heterogeneous hypoechoic plaque with a regular surface, indicating moderate internal carotid artery stenosis. Bottom, Low GSM on computerized analysis. **C**, Top, Simple homogeneous hyperechoic plaque with an acoustic shadow and a regular surface, indicating moderate internal carotid artery stenosis. Bottom, High GSM on computerized analysis.



vascular risk factors with the overall presence of carotid plaques and the presence of complex and simple plaques. Multiple logistic regression analysis with a 95% confidence interval was then applied to analyze vascular risk factor independent associations.

Results

Epidemiologic Characteristics

We studied 1655 consecutive patients, 762 male and 893 female. No statistical age difference was observed for sex (mean age ± SD: male, 66.6 ± 12.2 years; female, 66 ± 13.7 years).

Carotid Plaques and Types of Plaques

Of the 1655 patients, 705 (42.6%) had no carotid plaques; 611 (36.9%) had simple plaques; 274 (16.6%) had at least 1 complex plaque; and 65 (3.9%) had internal carotid occlusion.

Univariate Analysis of Vascular Risk Factors and Presence of Plaques

When considering all of the 1655 patients together for the presence or absence of carotid plaques, χ^2 analysis showed significant associations of all of the classic vascular risk factors with the presence of atherosclerotic lesions (older age, $P < .0001$; male sex, $P < .0001$; hypertension, $P < .0001$; diabetes, $P < .0001$; dyslipidemia, $P < .004$; and alcohol intake, $P < .02$).

Univariate and Multiple Logistic Regression Analysis of Vascular Risk Factors and Presence of Complex and Simple Plaques

χ^2 univariate analysis showed that a younger age ($P = .02$), male sex ($P = .02$), a history of CVD ($P < .0001$), hypertension ($P < .0001$), diabetes ($P < .0001$), and a greater IMT ($P < .0007$), were associated with complex plaques (Table 1).

Multiple logistic regression analysis showed the independent association of complex plaques with hypertension and diabetes. Moreover, higher IMT values were observed in complex than simple plaques. Results are reported in Table 1.

History of CVD

A history of CVD was observed more frequently in patients with complex plaques than in patients with simple plaques (Table 1).

Stenosis Percentage

The stenosis percentage was higher for complex plaques (complex, 60% ± 30%, versus simple, 15% ± 10%; $P < .0001$) because of selection criteria that classified plaques with a severe degree of stenosis (≥70%) in the major risk group. Interestingly, even after complex plaques with severe (≥70%) internal carotid artery stenosis and indications for carotid endarterectomy were excluded from the analysis and only patients with plaques that would have received medical treatment were considered, the complex plaques still had a higher degree of stenosis (complex, 30% ± 10%, versus simple, 15% ± 10%; $P < .0001$; Figure 2).

Table 1. Demographic Data and Vascular Risk Factor Distribution in Simple and Complex Plaques With Univariate and Multivariate Analyses

Characteristic	Simple Plaques	Complex Plaques	Univariate Analysis, *P*	Multivariate Analysis		
				β	OR (95% CI)	*P*
Age, y, mean ± SD	70.8 ± 9.3	73.2 ± 8.6	.02	.03		
Sex (male/female), %	52/48	56/44	.02	.27	1.3 (0.9–1.8)	NS
CVD history, %	25	33	<.0001	.98		
Smoking, %	52	56	NS	–.07	0.9 (0.6–1.3)	NS
Hypertension, %	69	81	<.0001	.53	1.7 (1.1–0.24)	.005
Diabetes, %	15	29	<.0001	.79	2.2 (1.5–3.2)	.000
Dyslipidemia, %	45	50	NS	.23	1.2 (0.9–1.7)	NS
Alcohol use, %	73	77	NS	.13	1.1 (0.7–1.6)	NS
IMT, mm	0.98	1.05	<.0007	1.0	2.8 (1.1–7.2)	.02

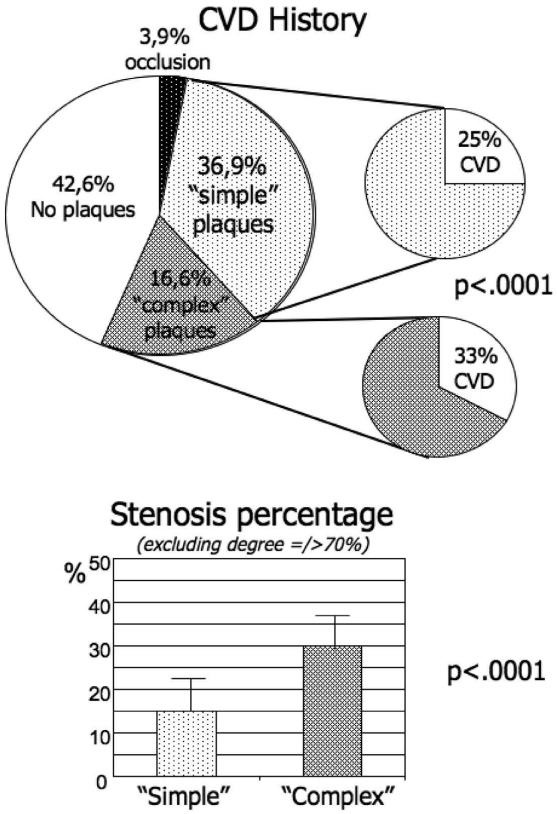
CI indicates confidence interval; NS, not significant (P > .05); and OR, odds ratio.

Discussion

Carotid imaging techniques are nowadays aimed at identifying vulnerable plaques to quantify the stroke risk accordingly. Duplex sonography is a reliable technique for assessing carotid stenosis that is easily and widely available in routine clinical practice, allowing evaluation of plaque morphologic characteristics.

Although the role of vascular risk factors in promoting atherosclerosis is well defined, less clear is the correlation of classic vascular risk factors with carotid plaque vulnerability. Elevated lipid plasma levels with reduced low-density lipoprotein cholesterol levels, postprandial triglyceride-rich lipoproteins,[16–18] and type 2 diabetes[19] are related to the presence of hypoechoic unstable carotid plaques by mechanisms probably connected to inflammation, inflammatory markers, and infections.

Figure 2. History of CVD and degree of stenosis in complex plaques at major risk of stroke and simple plaques at minor risk.



In our cohort of consecutive patients, we observed, as expected, a correlation of the classic vascular risk factors with the presence of carotid plaques. Nonetheless, the main observation in our series was the independent association of hypertension and diabetes with the presence of complex plaques at major risk of stroke. Hypertension and diabetes may play important roles in promoting local inflammation through still-unknown mechanisms, resulting in an increase of plaque activity. Plaque inflammation in these patients may be responsible for the infiltration of inflammatory plasma components, such as hemoglobin, oxidized low-density lipoprotein cholesterol, lipoprotein, glucose, advanced glycation end products, and inflammatory cells, into the extracellular matrix of the intima-media, leading to a heterogeneous hypoechoic structure and increasing plaque volume with a higher degree of stenosis. The histologic observation that symptomatic high-grade stenoses are usually heterogeneous, highly vascularized, and rich in inflammatory infiltrates with deep intraplaque hemorrhages confirms the importance of local inflammation in determining carotid plaque vulnerability.[25–27] Furthermore, detection of a higher IMT in patients with these complex plaques at major risk of stroke, being an expression of early atherosclerosis onset,[20,28] also supports the hypothesis of an active atherosclerotic process in these patients.

We also observed that patients with complex plaques at major risk of stroke had a higher frequency of a clinical symptomatic CVD history than patients with plaques at minor risk, as may have been predicted. Nonetheless, among all patients with complex plaques, two-thirds had not yet had symptomatic CVD. Furthermore, considering the degree of stenosis, even after patients with severe stenosis (≥70%) and indications for carotid surgery were excluded, the complex plaques still showed a higher stenosis percentage than simple plaques. In this regard, it is noteworthy to remember that asymptomatic and non–hemodynamically severe plaques should receive medical treatment, and their stability is thought to be improved by management of traditional cardiovascular risk factors or with pharmacologic agents that may exert effects on their pathophysiologic mecha-

nisms.[29] For these reasons, to identify those vulnerable lesions with a trend toward increased volume and instability and thus a major risk of stroke, strict sonographic surveillance for staging the lesions and monitoring their progression should be performed,[6] which might also aid in developing adequate preventive strategies.

In conclusion, we observed that complex plaques at major risk of stroke were independently associated with hypertension and diabetes. Patients with these atherosclerotic lesions should be carefully monitored and investigated for vascular risk factors for correct primary stroke prevention. Patients with complex lesions at major risk of stroke also had a more frequent history of CVD and a higher degree of stenosis than patients with simple plaques at minor risk, but two-thirds of these patients were still asymptomatic for CVD. Because these plaques have high potential to become symptomatic, frequent sonographic examinations should be performed to stage the lesions and monitor their progression, with identification of early specific preventive measures in cases of plaque evolution.

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