



NIHR HTA/BUPA Foundation/University of Oxford

Asymptomatic Carotid Surgery Trial (ACST-2)



Identifying the high-risk carotid plaque... A Herculaen task?

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Disclosure

Speaker name:

Athanasios D. Giannoukas.

- I have the following potential conflicts of interest to report:
 - Receipt of grants/research support
 - Receipt of honoraria and travel support
 - Participation in a company sponsored speakers' bureau
 - Employment in industry
 - Shareholder in a healthcare company
 - Owner of a healthcare company
- I do not have any potential conflict of interest



History





History

Carotid Plaque Histology Using Real-Time Ultrasonography

Clinical and Therapeutic Implications

Presented at the 11th Annual Meeting of the Society for Clinical Vascular Surgery, Palm Springs, California, March 23–27, 1983.

Linda M. Reilly, MD, San Francisco, California

Robert J. Lusby, MD, Sydney, Australia

Linda Hughes, RN, San Francisco, California

Linda D. Ferrell, MD, San Francisco, California

Ronald J. Stoney, MD, San Francisco, California

William K. Ehrenfeld, MD, San Francisco, California

The American Journal of Surgery

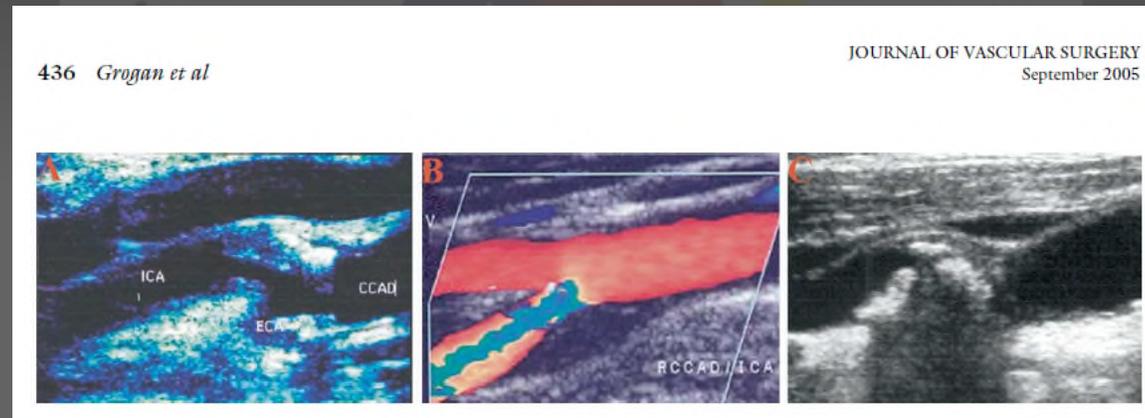
Preoperative ultrasound carotid imaging can be used to detect the histologic characteristics of plaque. Since recent clinicopathologic studies have implicated intraplaque hemorrhage and ulceration in symptomatic carotid disease, this information may be of value in choosing therapy, especially for the asymptomatic patient.



Early work

Association between plaque texture features and histological features:

- a low grey scale median (**GSM**) was associated with unstable plaques
- a high GSM with increased fibrous tissue and the presence of calcium



Grogan JK, Shaalan WE, Cheng H, Gewertz B, Desai T, Schwarze G, et al.. J Vasc Surg. 2005;42:435-41.
Sztajzel . Stroke 2005;36:741-5
El-Barghouti N, Nicolaidis AN, Tegos T, Geroulakos G. Int Angiol. 1996;15:300-6.



Recent work

Identification of Patients with a Histologically Unstable Carotid Plaque Using Ultrasonic Plaque Image Analysis

M.K. Salem ^{a,*}, M.J. Bown ^{a,b}, R.D. Sayers ^a, K. West ^c, D. Moore ^c, A. Nicolaides ^{d,e}, T.G. Robinson ^b, A.R. Naylor ^a

^aDepartment of Cardiovascular Sciences, University of Leicester, Leicester, UK

^bNIHR Leicester Cardiovascular Biomedical Research Unit, Leicester, UK

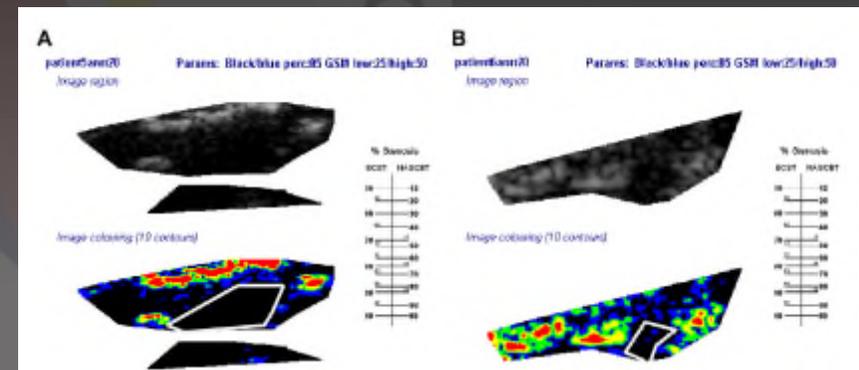
^cDepartment of Histopathology, University Hospitals Leicester, Leicester, UK

^dDepartment of Surgery, St George's University of London, London, UK

^eUniversity of Nicosia Medical School, Nicosia, Cyprus

Histologically unstable plaques:

- Low GSM
- Large plaque area
- Juxtaluminal black area (JBA) > 8 mm²



Conclusions: Computerized plaque analysis has the potential to identify patients with histologically unstable carotid plaques. This model requires validation, but offers the potential to influence patient selection for emergency interventions and the monitoring of medical therapy.



Recent work

Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification

Andrew N. Nicolaides, MS, FRCS, PhD (Hon),^a Stavros K. Kakkos, MD, MSc, PhD, DIC,^a Efthymoulos Kyriacou, BSc, PhD,^b Maura Griffin, MSc, DIC, PhD,^a Michael Sabetai, MD, FRCS, PhD,^a Dafydd J. Thomas, MD, PhD,^c Thomas Tegos, MD, PhD,^a George Geroulakos, MD, PhD,^{a,d} Nicos Labropoulos, PhD, DIC, RVT,^e Caroline J. Doré, BSc,^f Tim P. Morris, MSc,^f Ross Naylor, MD, FRCS,^g and Anne L. Abbott, MB, BS, FRACP, PhD,^{h,i} for the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group, *London and Leicester, United Kingdom; Limassol, Cyprus; Stony Brook, NY; and Melbourne, Australia*

CLINICAL RESEARCH STUDIES

From the Society for Vascular Surgery

The size of juxtaluminal hypoechoic area in ultrasound images of asymptomatic carotid plaques predicts the occurrence of stroke

Stavros K. Kakkos, MD, PhD, RVT,^a Maura B. Griffin, PhD,^a Andrew N. Nicolaides, FRCS, PhD,^a Efthymoulos Kyriacou, PhD,^b Michael M. Sabetai, MD, PhD,^a Thomas Tegos, MD, PhD,^a Gregory C. Makris, MD,^{a,c} Dafydd J. Thomas, MD, FRCP,^a and George Geroulakos, MD, PhD,^{a,c} for the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group,^a *London, United Kingdom; and Limassol, Cyprus*

Table. Cox proportional hazards models including JBA and other plaque features known to be associated with increased risk^a

Variable	β	HR	95% CI	P
Model A				
JBA (<4, 4-8, 8-10, >10 mm ²)	0.816	2.26	1.84-2.78	<.001
Stenosis (50-69, 70-89, 90-99%)	0.241	1.27	0.98-1.66	.073
DWA (present, absent)	0.883	2.42	1.52-3.85	<.001
History of contralateral TIA or stroke (present, absent)	0.518	1.68	1.14-2.47	.008
GSM (<15, 15-30, >30)	-0.041	0.96	0.72-1.27	.776
Plaque area (<40, 40-80, >80 mm ²)	0.099	1.04	0.83-1.47	.502
Model B				
JBA (4, 4-8, 8-10, >10 mm ²)	0.773	2.16	1.58-2.97	<.001
Stenosis (50-69, 70-89, 90-99%)	0.465	1.59	1.06-2.38	.025
DWA (present, absent)	0.619	1.86	0.98-3.51	.057
History of contralateral TIA or stroke (present, absent)	0.793	2.21	1.28-3.61	.004
GSM (<15, 15-30, >30)	0.163	1.18	0.75 to 1.83	.471
Plaque area (<40, 40-80, >80 mm ²)	0.051	1.05	0.68-1.62	.818
Model C				
JBA (4, 4-8, 8-10, >10 mm ²)	0.853	2.34	1.89-2.91	<.001
Stenosis (50-69, 70-89, 90-99%)	0.462	1.59	1.06-2.37	.023
DWA (present, absent)	0.582	1.90	0.98-3.27	.059
History of contralateral TIA or stroke (present, absent)	0.788	2.20	1.27-3.79	.005



Aim

To determine the association of ultrasonic plaque texture features:

- severity of stenosis
- GSM
- plaque area
- JBA
- discrete white areas (DWA)

with established histological features of plaque instability



Material and Methods

- 70 carotid bifurcation plaques taken after elective carotid endarterectomy for histologic analysis
 - 20 symptomatic: 2 stroke and 18 transient ischemia attack
 - 50 asymptomatic
- Pre-op (3-5 days) carotid US scanning with the intention to proceed with plaque analysis
- Both, the physician undertaken the US evaluation and the histopathologist were not aware of the clinical status of the patients



US Image normalisation

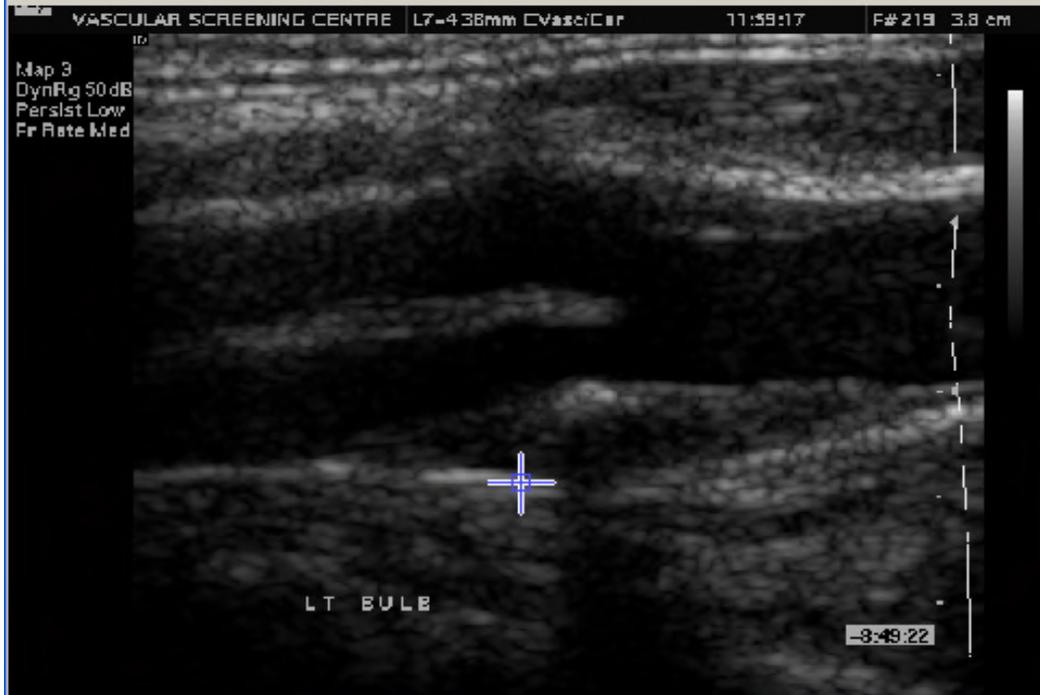
Image histogram normalisation



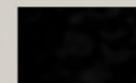
File Help

Initial image

Normalised image



Blood area



Blood Med.
2.0

Adventitia area



Advent. Med.
93.0

Select drive Select BWV Image

- A:
 - B:
 - C:
 - D:
 - E:
 - F:
 - G:
 - H:
- CARBULB17a.TIF
 - CARBULB17b.TIF
 - CARBULB17cTS.TIF
 - CARBULB18.TIF
 - CARBULB18a.TIF
 - CARBULB19.TIF
 - CARBULB19a.TIF
 - CARBULB19bTS.TIF
 - CARBULB1a.TIF
 - CARBULB2.TIF
 - CARBULB20.TIF

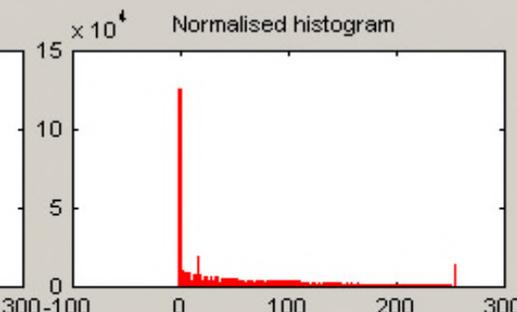
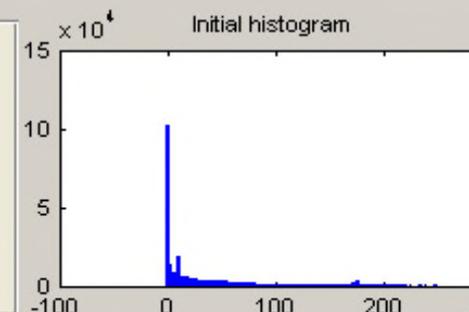
Select Action

Zoom in / out

Start normalisation

HELP

In order to save the file:
Press save file button



C:\Documents and Settings\Andreas\My Documents\Course Images 1

Save File

Close

Texture feature extraction

Use of GSM software (LifeQ Medical)

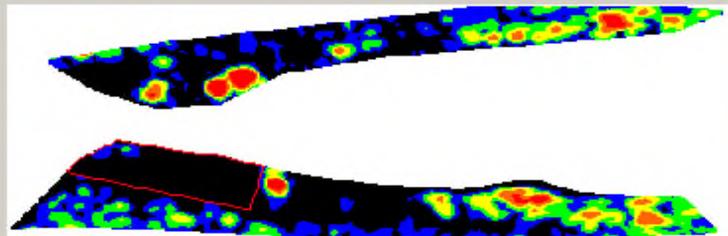
Plaque parameters

File Help

Image region



Image colouring (10 contours)



Zoom

Meas. Dark area close to lumen

1 comp. All plaque

Perc. of dark area: 19.7 11.55

Dark area mm2: 8.3

Dark area

Dark area

Close to lumen

Yes

Patient status

A (Asym)

Discrete white areas

Yes

Type of plaque

Type 3

Percent Stenosis 1-99%

90

HELP

In order to calculate the parameters for a plaque file, double click on the appropriate ...pl (version 1.x) or ...plq(version 2.x) file

Select drive

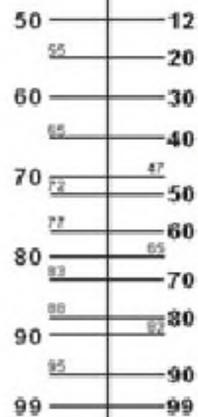
- A: 10rc0bw.tif
- B: 10rc0bwn.tif
- C: 10rc0bwnr.plq
- D: 10rc0bwnr.scl
- E: 10rc0bwnr.tif
- F: 10rc0bwnrr10.plq
- G: 10rc0bwnrr20.plq
- H: 10rc0bwnrr20_plq.tif
- 10rc0bwnrr20r15.plq

C:\Documents and Settings\Andreas\My Documents\ACSRS Images\110

Filename:10rc0bwnrr20.plq

% Stenosis

ECST NASCET



Histogram measures

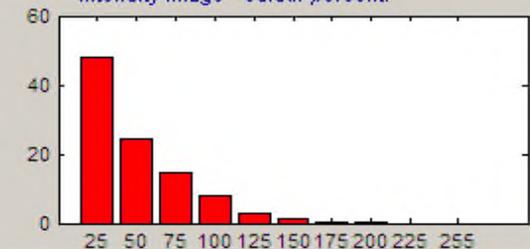
Kurtosis

1.69901
Total number of pixels
28762
Plaque area mm2
71.91
Perc. of pix below lev.30
54.24%
Perc. of pix below lev.50
72.49%

Contours

Black 48.01%
24.48%
14.85%
7.809%
3.056%
1.175%
0.4033%
0.2156%
White 0%
0%

Intensity image - colour percent.



Texture measures

SGLDM measures

Ang.S.Mom 0.00749869
Contrast 49.6491
Correl 0.977644
Variance 1108.61
Homoge. 0.275297
Sum Aver. 73.1522
Sum Var. 4384.8
Sum Entr. 5.1589
Entropy 7.38066
Diff. 25.3631
Diff. Entr. 2.64608
Inf.Meas1 -0.358678
Inf.Meas2 0.978652

First ord. stats

Mean 35.4664
Varian. 1096.58
Median 26.9169
Skewn. 1.21657
Energy 0.0198508
Entropy 4.49302

GLDM measures

Homog. 0.275695
Contr. 49.4785
Energy 0.0921141
Entropy 2.66801
Mean 4.81659

Runlength meas.

SRE 0.931959
LRE 1.66927
GLD 280.081
RLD 20389.3
RP 23.6423

Fourier power spec.

Radial 2925.06
Angular 2699.94

Save Parameters

ACSRS eq. risk

Close



Material and Methods

➤ **US characteristics used :**

- ✓ **GSM**
- ✓ **plaque area** expressed in mm^2
- ✓ **presence of DWAs** having grey scale values >124
- ✓ **presence of a JBA** defined as an area greater than 8 mm^2 adjacent to the lumen with pixels having a grey scale value < 25)



Unstable atheroma on histopathology

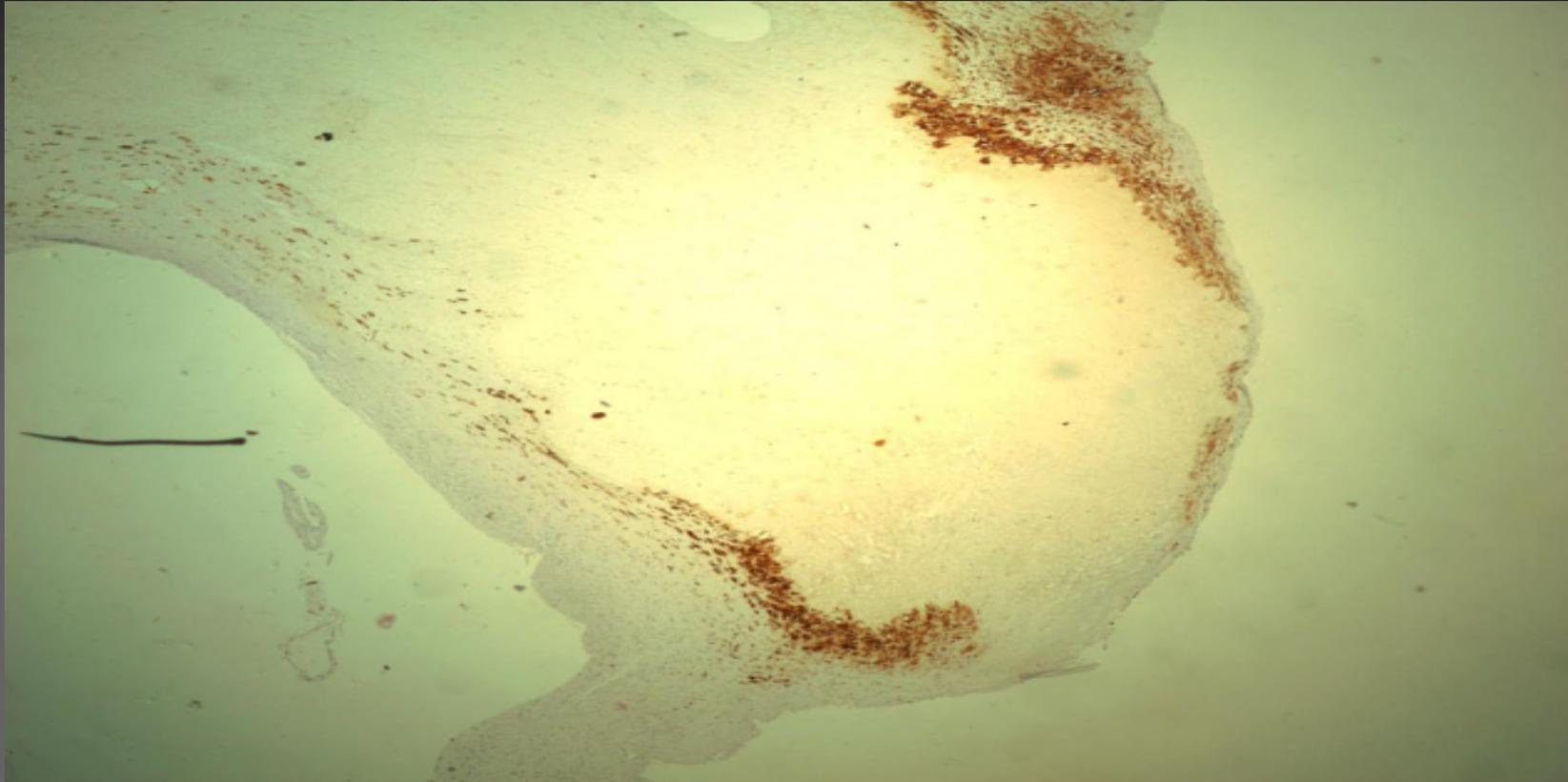
- Presence of abundant macrophages
- Presence of only few SMCs because inflammatory cells increase the apoptosis due to their damage from the macrophages.

Material and Methods



CD68 protein is a macrophage marker encountered in the presence of carotid plaque inflammation.

- absence (0)
- small scattered collections (1)
- masses of moderate cellular density (2)
- confluent hypercellular areas (3)





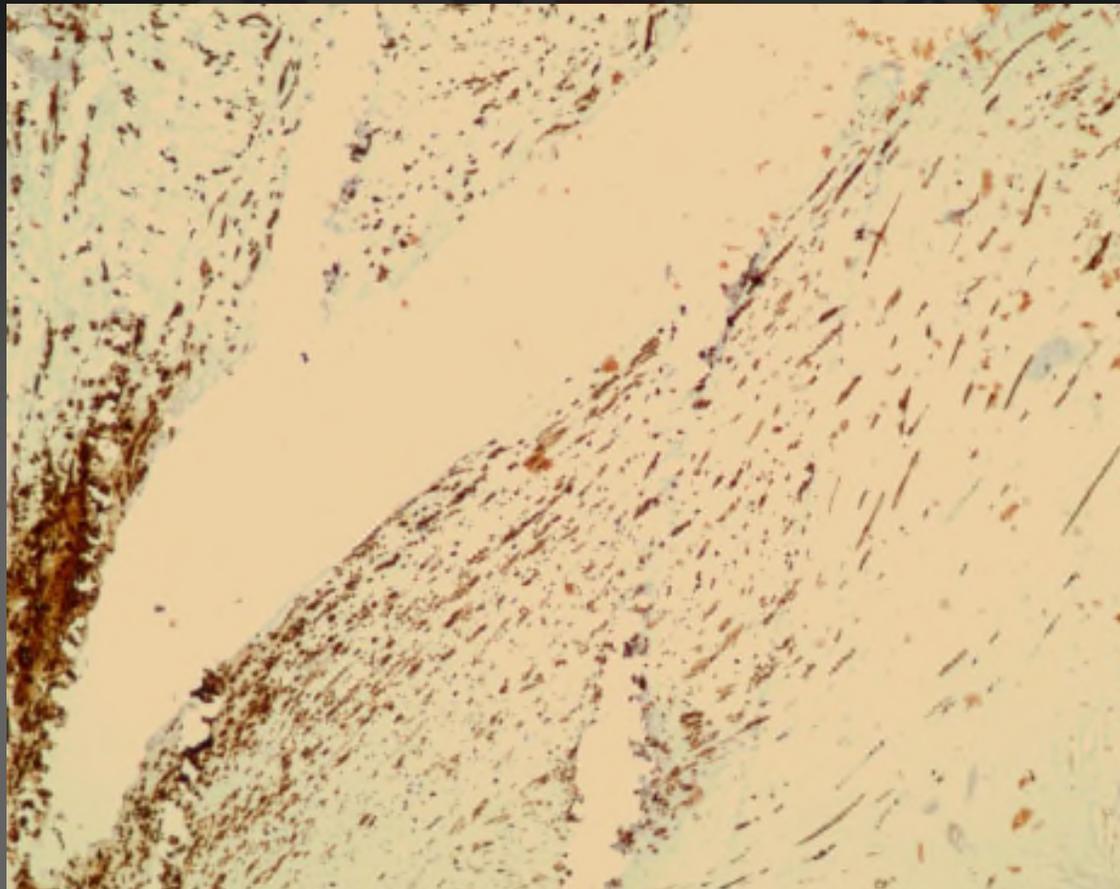
Material and Methods



Smooth muscle cells (SMCs) with emphasis on the density and thickness:



- thin loose arrangement (1)
- intermediate arrangement (2)
- thick, dense band (3)





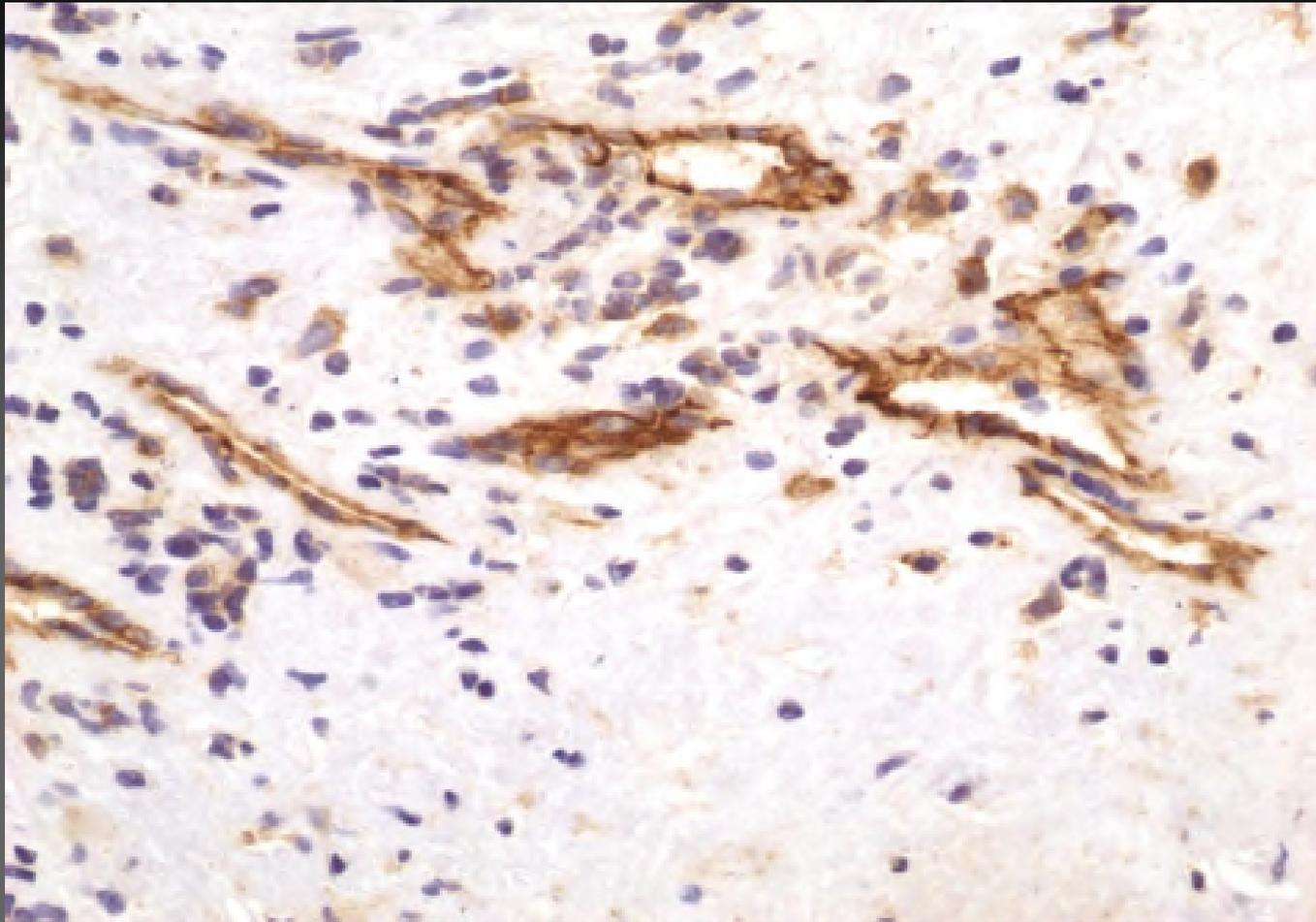
Material and Methods



The presence and degree of **neoangiogenesis**



- Presence of microvessels in the atherosclerotic plaque with **anti-CD 31 antibodies**





Material and Methods

Plaques were also classified according to:

- **Fibrous cap** (thin or thick)
- **Lipid core** (small, medium, large)
- **Plaque rupture** (present or absent)
- **Intra-plaque hemorrhage** (present or absent)



Results

Risk factors

Risk factors and medical treatment	All plaques (70)	Asymptomatic plaques (n=50)	Symptomatic plaques (n=20)	P*	Stable plaque (n=34)	Unstable plaque (n=36)	P*
Age (in years)	69 ± 7.6	68.7 ± 7.8	69.8 ± 7.4	.560	69.8 ± 8.3	68.2 ± 7.0	.402
Gender (male/female)	51/19	11/39	8/12	.126	25/9	26/10	.902
Total cholesterol (in mg/dL)	230 ± 29	225 ± 28	242 ± 27	.023	237 ± 27	223 ± 28	.044
Smoking	40/70 (57%)	26/50 (52%)	14/20 (70%)	.053	17/34 (50%)	23/36 (64%)	.344
Diabetes	17/70 (24%)	14/50 (28%)	3/20 (15%)	.252	11/34 (32%)	6/36 (17%)	.126
Hypertension	49/70 (70%)	37/50 (74%)	12/20 (60%)	.631	21/34 (62%)	28/36 (78%)	.423
CAD	49/70 (70%)	37/50 (74%)	12/20 (60%)	.631	22/34 (65%)	27/36 (70%)	.443
Creatinine (in mg/dL)	1.00 ± 0.21	0.99 ± 0.20	1.02 ± 0.23	.915	1.00 ± 0.24	0.99 ± 0.18	.911
Ipsilateral Carotid Stenosis	86.2 ± 9.5	86.1 ± 8.8	86.3 ± 11.3	.912	83.2 ± 10.3	89.0 ± 7.7	.009
Contralateral caortid stenosis	25/70 (36%)	15/50 (30%)	12/20 (60%)	.240	9/34 (27%)	16/36 (44%)	.134
Antiplatelet treatment	25/70 (36%)	20/50 (40%)	5/20 (25%)	.237	9/34 (26%)	16/36 (44%)	.117
Statin therapy	35/70 (50%)	32/50 (64%)	3/20 (15%)	< .001	19/34 (56%)	16/36 (44%)	.339



Results

➤ **Low GSM** was associated with histologically unstable plaques:

- **thin fibrous cap**
- **a large lipid core**
- **a small number of SMC**
- **increased inflammation** (increased number of macrophages and neovascularization)
- **intraplaque hemorrhage**
- **plaque rupture**



Results

High numbers of SMC were associated:

- a high GSM
- histologically stable plaques



Results

- All histological features characterizing unstable plaques except fibrous cap thickness were associated with the presence of DWA



Results

A major finding of our study :

- lack of association of **plaque area** with characteristics of **plaque instability**

Possible explanation:

- ❖ risk of plaque rupture in large plaques may not related mostly to its histological structure but it may be inherent to its size and particularly its length
- ❖ The role of biomechanical forces in the induction of plaque fatigue and rupture has been emphasized for some time



Results



Possible explanation role of biomechanical forces in the induction of plaque fatigue and rupture :



- **High plaque strain** (deformability due to high pulse pressure and blood velocity) and **high stress** (associated forces)  **plaque rupture**

Differences between motion measurements extracted from symptomatic and asymptomatic plaques have been demonstrated

Feasibility of computing carotid plaque strain measurements from routine B-mode

Future studies with plaque motion analysis



Limitations

- **Statin therapy** administered to 64% of asymptomatic and only 15% of symptomatic patients
- **Small number** of patients included
- Variety of average **waiting time between referral and operation** (ranging from 2 to 4 weeks) in the symptomatic patients

Larger prospective studies are needed to support the observations of our study



Conclusions

- A number of **key ultrasonic texture features** previously shown to be able to stratify asymptomatic patients into different classes of stroke risk have a strong association with **established histological features of plaque instability**
- Plaque area did not have any association with **established histological features of plaque instability**
- These findings provide further validation of the usefulness of ultrasonic analysis of carotid atheroma in stroke risk stratification



THANK YOU



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