Teaching Course 5

Advanced neurosonology - Level 3

Carotid artery stenosis grading and examination of the vulnerable plaque

Fabienne Perren
Geneva, Switzerland

Email: fabienne.perren@hcuge.ch
1. Introduction
2. Grading carotid artery stenosis
3. Plaque formation, vulnerable plaque
4. Conclusions

Conflict of interest:
The author has no conflict of interest in relation to this manuscript.
OUTLINE

1. Introduction

2. Grading carotid artery stenosis

3. Plaque formation, vulnerable plaque

4. Conclusions

• Duplex Ultrasound (DUS) has the advantage to be noninvasive, safe, inexpensive, and to be a rapid and repeatable applicable bedside method.

• It is an important tool in the characterization of plaque structure and the assessment of stenosis of the extracranial vessels.

• DUS main drawbacks are its dependency on the examiner’s experience and the anatomical inaccessibility of certain vessel regions.
• **Atherosclerotic macroangiopathy** of the extracranial internal carotid artery (ICA) is a **relevant risk factor** for anterior cerebral circulation ischemia.

• **In up to 20%**, ischemic **strokes** result from **stenotic processes** of extracranial vessels supplying the brain, especially from the **internal carotid artery** or of the carotid bifurcation\(^1,2\).

---


---

• **Mechanism of stroke** seems here to be attributable to the degree of stenosis and to fissured or ruptured plaques initiating thromboembolism\(^3,4\).

• However, it remains unclear **which specific factor** mainly causes an increased risk of stroke.

---

• Approximately 5–10% of all individuals aged 65 years or over suffer from an asymptomatic ICA stenosis of 50% luminal narrowing or more\textsuperscript{1}.

• Approximately 10–15% of all ischemic strokes and TIsAs occur in the territory of a severely stenosed ICA\textsuperscript{1,2}.


• The annual risk of a major stroke varies from 1 to 3.2% in cases of luminal narrowing ranging from 50 to 99%\textsuperscript{1-4}.

• This risk remains almost stable over a long period of time\textsuperscript{5}.

• An increasing degree of luminal narrowing is associated with an increasing risk of stroke in asymptomatic ICA stenosis. For every 10% increase in luminal narrowing, the stroke risk increases by nearly 31%, or 0.6% (in absolute terms) per year\(^6\).

• Stenoses > 95% luminal narrowing may be associated with a reduced stroke risk in comparison with stenosis of between 80 and 95\%\(^6\).


GRADE OF ICA STENOSIS

3 Principal methods to determine the grade of the ICA stenosis:

• NASCET: distal grade of stenosis (CAVE: low grade stenoses)

• ECST: local grade of stenosis

• CC: grade of stenosis between the stenosed diameter and the proximal nonaffected CCA

ECST and NASCET studies, 1991
• It is important to note that the **NASCET method** describes predominantly the *hemodynamic* significance of ICA stenosis (relation of the inflow to outflow diameter), whereas the **ESCT method** reflects more the amount of atherosclerotic tissue at the stenosed segment.

• The degree of luminal narrowing determined can vary significantly between the two different methods. In most cases, the ECST method results in a 10–30% higher degree of ICA stenosis, especially in the middle range (i.e., 50–80%) ¹.


---

**Grading Carotid Stenosis Using Ultrasonic Methods**

Gerhard-Michael von Reutern, MD, PhD; Michael-Wolfgang Goertler, MD, PhD; Natan M. Bornstein, MD; Massimo Del Sette, MD; David H. Evans, PhD, DSc; Andreas Hetzel, MD, PhD; Manfred Kaps, MD, PhD; Fabienne Perren, MD, PhD; Alexander Razumovsky, PhD; Toshiyuki Shiogai, MD, PhD; Ekaterina Titianova, MD, PhD, DSc; Pavel Traubner, MD, PhD; Narayanaswamy Venketasubramanian, MD; Lawrence K.S. Wong, MD; Masahiro Yasaka, MD, PhD; on behalf of the Neurosonology Research Group of the World Federation of Neurology

(Stroke. 2012;43:916-921.)
BACKGROUND

- Reliability of Doppler/duplex sonography to determine the degree of an ICA stenosis
- No universally accepted set of criteria to measure the degree of stenosis
- No consensus about the relative weight of different criteria

ASSESSMENT OF MORPHOLOGY

- The relationship between area and diameter reduction depends on the type of stenosis (concentric or eccentric)
ASSESSMENT OF MORPHOLOGY

- In eccentric carotid artery stenosis, diameter and area reduction are similar.
- However, in concentric narrowing, degree of stenosis measured in percentage reduction is higher than the measured diameter reduction.

ASSESSMENT OF HEMODYNAMIC EFFECT

- Arterial narrowing leads to locally increased velocities.
- A hemodynamic effect is reached when pressure and flow volume are diminished in the poststenotic segment.

\[ \text{Re} = \frac{VD}{r} \]

- Where: \( V \) = BFV (cm/s), \( D \) = diameter (cm), \( r \) = blood density.

\[ \text{Re} = 2000 \]
STENOSIS AND FLOW PROFILE

The number of Reynolds allows to characterize flow profile and to determine a critical value for a turbulent blood flow (< 2000).

\[Re = \frac{VD}{r/h}\]

- Where: \(V\) = BFV (cm/s); \(D\) = diameter (cm); \(r\) = blood density; \(h\) = blood viscosity (g.cm\(^{-3}\))

\[Re = 26 \sqrt{D}\]

- Irregular, eccentric, >70% stenosis

ASSESSMENT OF HEMODYNAMIC EFFECT

- This effect is clinically important because the probability of having a complicated plaque structure prone to embolism is higher in this situation.

- There is the risk of ischemia because of an insufficient blood supply.
ASSESSMENT OF HEMODYNAMIC EFFECT

- Flow velocity as measured by means of Doppler sonography correlates with the narrowing measured in area reduction. The correlation of velocity and the degree of stenosis is demonstrated by the "Spencer's curve".1,2


- Vessel narrowing is directly correlated with raising flow velocities, but it is not linear over the whole range of stenosis grades: in very high grade stenosis and near occlusion flow velocity drops to normal or below normal values.

- BFV remain constant until a 75-80% diameter reduction.

Relationship of stenosis grade and SBFV within the stenosis

• There are many reasons why PSV, whatever threshold is used, is frequently in disagreement with the angiographic result and is of limited value taken alone:

• First, there is the morphology of the stenosis as discussed (area versus diameter, irregularities ill-represented by all imaging modalities).

• Second, there is ambiguity of the “Spencer’s curve,” with the possibility of the same velocity in a moderate stenosis and a nearly occluded artery.1,2 Velocity in a stenosis increases with increasing degree of stenosis but decreases in situations of near occlusion.

\[ V = \frac{c (F_r - F_0)}{2 F_0 \cos \alpha} \]


• Third, there are errors and different conventions in measuring the angle of insonation needed for converting recorded Doppler frequencies into velocities.1 Due to the cosine function (Doppler equation) the possible error converting Doppler shift to velocity increases with increasing Doppler angle.
• The angle can be estimated fairly well in laminar flow conditions but it is difficult with disturbed flow, where stream lines differ from the vessel course.

• Helical organization of poststenotic disturbed flow (or because of vessel curvature) can lead to overestimation of velocities because of incorrect estimation of the angle, even using color flow imaging as a guide.

- Fourth, there is the influence of collateral flow. Velocities in a stenosis depend on collateral flow toward the territory supplied by the stenosed artery.

- Collateral flow via the circle of Willis and less effectively via the ophthalmic artery is only present in a hemodynamically significant stenosis.

- The higher the capacity of this collateral network, the less the poststenotic pressure decrease and, consequently, the intrastenotic velocity. Because there is a considerable variation of the circle of Willis, its influence on the PSV is different from patient to patient.

- The same holds true for the PSV contralateral to an internal carotid artery occlusion.

• Fifth, there is the technical problems of spectrum analysis.

• The Doppler spectrum generated by a short stenosis is typically composed by high-frequency (velocity) components representing the jet, and low-frequency ones attributable to vortices and flow separation.

• The relative weight of the parameter for the hemodynamic effect and the measured flow velocities. High-frequency components can be so low that they will not be displayed without special high-pass filtering or setting of the gain. This can lead to underestimation of the PSV.¹


ADDITIONAL CRITERIA

• Poststenotic flow velocity and distal caliber assessment as criteria of high grade proximal internal carotid artery stenosis

Background:
Peak systolic velocity (PSV) of the distal internal carotid artery (ICA) <50 cm/s was introduced as a criterion to distinguish 80% stenosis (NASCET) from lower grade stenosis (NSRG consensus).

A reduced caliber of the ICA due to the poststenotic pressure reduction could also be a criterion for high grade ICA stenosis.

• In the present study PSV and distal calibers in patients with and without high-grade stenosis were measured in order to assess the value of these criteria.
Methods

110 patients with vascular risk factors without ICA stenosis

54 patients with ICA stenosis (of whom 21 patients with a unilateral proximal high grade ICA stenosis)

underwent prospectively CCDS. PSV was measured at least 2 cm distal from the bifurcation. The distal diameter was measured during systole in B-Mode or B-Flow.

Graduation was made according to the NSRG consensus (≥ or <80%).

ADDITIONAL CRITERIA

Results

Distal PSV of the ICA with high-grade (>80%) stenosis (p<0,00001 compared to the two other groups: without stenosis vs with stenosis <80%).

The distal diameter with high-grade >80% stenosis (p<0,0001 compared to the two other groups).

ROC analysis finds for the distal PSV<50cm/s (sensitivity 0,8, specificity 0,89).

For the distal ICA diameter the cut off is <3mm (sensitivity 0,82; specificity 1,0).
ADDITIONAL CRITERIA

Conclusions

- A distal PSV of ≥50cm/s is a useful value to exclude high-grade stenosis.
- In our study the measurement of the distal calibre of the ICA showed a good sensitivity and specificity.
- In none of the vessels without stenosis a diameter of <3mm was found, but in 86% of the high-grade stenosis.

MAIN STEPS OF GRADING

Low-Degree Stenosis up to 40% (NASCET)

- This is the domain of B-mode imaging in the longitudinal and cross-sectional planes.
- Velocity measurement rules out a more severe stenosis sometimes suggested by an inappropriate sectional plane.
- It is therefore recommended to measure, in addition to the reduction of diameter in percent, the thickness and length of the plaque as well as the residual lumen.
- And to describe the composition and the surface of the plaque.
MAIN STEPS OF GRADING

Moderate Stenosis 50% to 60% (NASCET) (<80% ECST)

• This is a class of stenosis in which local increase of velocity, color flow, and B-mode imaging can be combined for grading. PSV is, in general, 230 cm/s.

CAVE: Collateral flow is not present.

MAIN STEPS OF GRADING

Hemodynamically Relevant Stenosis >70% (NASCET) (>80% ECST)

• This is the domain of combined hemodynamic criteria, such as increased PSV or end-diastolic velocity or the “carotid ratio” (ratio of internal to common carotid PSV), but there is a considerable overlap with moderate stenoses.

• Collateral flow is demonstrated by examining the ophthalmic artery branches (Doppler ophthalmic test), the ACA/ACoA, proving cross-flow or the P1 segment of the PCA, indicating collateral flow through the PCoA.

• In case of established collateral flow, hemodynamic relevance of the stenosis is proven and it can be classified as high-degree irrespective of the intrastenotic PSV).¹

Hemodynamically Relevant Stenosis >70% (NASCET)

- **Poststenotic flow velocity** in the segment distal to the disturbed flow field is another criterion. In case of a clear reduction of signal pulsatility and poststenotic velocity (e.g., 30 cm/s PSV),

- **The degree of reduction** of poststenotic flow velocity (as a result of reduced flow volume) helps to differentiate between 70% (severe) and 80% to 90% (very severe) stenosis, a differentiation possible based only on PSV values.

- A comparison with the unaffected contralateral internal carotid artery is helpful to appreciate poststenotic flow reduction.

DIFFICULTIES / PITFALLS

- Shadowing: calcified plaque
- Hypoechoic plaque
- Tandem stenosis or an ICA hyperperfusion (Carotid ratio index: PSV ICA/PSV CCA)
- High bifurcation or status post endarterectomy (coronal)
In combination with further criteria it is possible to decide whether a measured PSV represents a less or more severe stenosis within the scatter range.

The main advantage of a multi-parametric grading of ICA stenoses is the synergetic effect of the different single criterion.

Combining these ultrasound criteria, duplex ultrasound allows reliable grading of carotid stenoses as a basis for decision.
• In clinical practice, divergent results of gradings between raters and methods occur. They potentially lead to different therapeutic consequences.

• Due to an increased application of CTA in patients with AIS, the comparison between DUS and CTA in grading proximal ICA stenosis and inter-methodical inconsistencies of results are relevant matters in the daily work of neurovascular units.

• In the context of the 2010 (DEGUM) AND 2012 (NSRG) revised DUS criteria, The correlation of proximal ICA stenosis gradings between DUS and CTA using NASCET and ECST definitions was systematically analyzed by the authors.

• In addition, interrater reliability (IR) was assessed for both methods.

---

Table 1. DUS criteria for grading proximal ICA stenoses

<table>
<thead>
<tr>
<th>Degree of stenosis (DOS) of the proximal internal carotid artery (ICA)</th>
<th>Defined by NASCET (% ±5)</th>
<th>Defined by ECST (% ±5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>20–40</td>
<td>50</td>
</tr>
<tr>
<td>Main criteria [1–5]</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>1. B-mode image</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2. Color doppler image</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3. Intermesial PSV (cm/s)</td>
<td>~200</td>
<td>~250</td>
</tr>
<tr>
<td>4. Post-stenotic PSV (cm/s)</td>
<td>&gt;50</td>
<td>50</td>
</tr>
<tr>
<td>5. Perivascular tissue vibration</td>
<td>(++)</td>
<td>++</td>
</tr>
<tr>
<td>Supplementary criteria [6–10]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Pre-stenotic EDV reduction (CCA)</td>
<td>(++)</td>
<td>++</td>
</tr>
<tr>
<td>7. Post-stenotic flow distorsion</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8. Intramesial EDV (cm/s)</td>
<td>&lt;100</td>
<td>&lt;100</td>
</tr>
<tr>
<td>9. Perivascular tissue vibration</td>
<td>(++)</td>
<td>++</td>
</tr>
<tr>
<td>10. PSV ratio (ICA/CCA)</td>
<td>≥7</td>
<td>7</td>
</tr>
</tbody>
</table>

Comments to Criteria 1–10: Criterion 1 documentation of width, length and morphology of vessel wall changes. Criterion 2 essential to detect local flow disturbances (‘‘damping’’) to dissiminate between non-stenotic plaque and low grade stenosis, to show flow direction and to diagnose vessel occlusion. Criterion 3 angle corrected (<60°) measurement of jet stream velocity in or directly cranial to stenosis, limited validity in short (<1 cm) and long (>1 cm), low (<50%) and high (>90%) grade-classes as well as in multiple vessel processes. Criterion 4 measurement at the most distinct extramural position outside jet stream and free of post-stenotic flow disturbances. If necessary by application of a curved or phased array transducer. Criterion 5 confirms via non-communications anterior-posterior or supra-aortic artery, requires careful inspection because of frequent anatomical variants. Criterion 6 synonym ‘‘increased pulsatility’’ varies according to collateral status, limited value in multiple vessel processes (i.e., tandem stenosis, contralateral occlusion). Criterion 7 not pathologial, therefore only useful in combination with other criteria. Criterion 8 useful when intramesial PSV (Criterion 3) not measurable. Criterion 9 synonym ‘‘Confetti Sign’’, measurement immediately cranial to stenosis with low pulse repetition frequency (PW). Criterion 10 useful for the assessment of carotid artery tandem stenoses, hyperplasia and primary (constitutively) narrow vessels.

ICA internal carotid artery, NASCET North American Symptomatic Carotid Endarterectomy Trial, ECST European Carotid Surgery Trial, PSV peak systolic velocity, EDV end-diastolic velocity, CCA common carotid artery

* adapted and translated from [9].
• **For NASCET criteria**, stenoses between 1 and 49 % were defined as low grade, between 50 and 69 % as moderate grade and between 70 and 99 % as high grade.

• **For ECST criteria**, stenoses between 1 and 69 % were defined as low grade, between 70 and 79 % as moderate grade and 80–99 % as high grade.

**Statistical analysis**

The linear weighted kappa statistic (κw) was used to determine IR among raters and agreement among methods. Weighted kappa values 0.00–0.20 indicated slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial and 0.80 almost perfect agreements.
### Statistical Analysis

The linear weighted kappa statistic ($\kappa_w$) was used to determine IR among raters and agreement among methods. Weighted kappa values $\lessapprox 0.20$ indicated slight, $0.21–0.40$ fair, $0.41–0.60$ moderate, $0.61–0.80$ substantial and $\geq 0.80$ almost perfect agreements.

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>1–49%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>80%</th>
<th>90%</th>
<th>Occluded</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CTA observers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DUS observers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Normal: 16
- 1–49%: 16
- 50%: 23
- 60%: 6
- 70%: 1
- 80%: 1
- 90%: 0
- Occluded: 0

- Total: 26
- 1–49%: 31
- 50%: 10
- 60%: 6
- 70%: 1
- 80%: 1
- 90%: 0
- Occluded: 32

### Diagrams

- **A**: Freehand 3D US
- **B**: Imaging modality
- **C**: Anatomical structure
Freehand 3D US

Table 1. Intra-rater, inter-rater and inter-method agreement of 3D ultrasound (3DUS) for quantification of internal carotid artery stenosis (ICAS).

<table>
<thead>
<tr>
<th></th>
<th>Intra-rater agreement (ICC)</th>
<th>Inter-rater agreement (ICC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ex1 (1. &amp; 2. scan)</td>
<td>1 scan</td>
</tr>
<tr>
<td>B-mode 3DUS: CSA reduction percentage</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>B-mode 3DUS: diameter reduction percentage</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Power-mode 3DUS: CSA reduction percentage</td>
<td>0.88* (CI: 0.79-0.94)</td>
<td>0.78* (CI: 0.62-0.89)</td>
</tr>
<tr>
<td>Power-mode 3DUS: diameter reduction percentage</td>
<td>0.88* (CI: 0.79-0.94)</td>
<td>0.78* (CI: 0.62-0.89)</td>
</tr>
</tbody>
</table>

Reference standard for grading carotid stenosis was 2D colour-coded duplex ultrasonography. Stenotic value in 3D reconstructed CAS was calculated as distal diameter respectively distal cross-sectional area (CSA) reduction percentage. ICC intra-class correlation coefficient, Ex1 examiner 1, Ex2 examiner 2, CI 95% confidence interval of the intra-class correlation coefficient, n.a. non available. * indicates statistical significance i.e. p < 0.05.
• Identifying patients with less severe stenosis and without symptoms who may benefit from CEA/TSA continues to be a challenge.
• In recent years, evaluation of the carotid plaque in a different manner placing less emphasis on the severity of the stenosis and more emphasis on the morphology and functional characteristics of the plaque.

Fig 2. Computed tomography (CT) angiography correlates with carotid angiography in the identification of carotid luminal stenosis in this linear regression analysis (solid line).
Identifying patients with less severe stenosis and without symptoms who may benefit from CEA/TSA continues to be a challenge.

In recent years, evaluation of the carotid plaque in a different manner placing less emphasis on the severity of the stenosis and more emphasis on the morphology and functional characteristics of the plaque.

Table V. Suggested velocity criteria defining stenoses in the stented carotid artery compared to criteria for the native carotid artery used at our institution

<table>
<thead>
<tr>
<th>Stenosis %</th>
<th>Stented carotid artery</th>
<th>Native carotid artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10%</td>
<td>PSV ≤ 130 cm/s and ICA/CCA ratio ≤ 2.15</td>
<td>PSV ≤ 1.80 cm/s</td>
</tr>
<tr>
<td>10-30%</td>
<td>PSV 150-210 cm/s</td>
<td>PSV 190-249 cm/s</td>
</tr>
<tr>
<td>30-50%</td>
<td>PSV 220-289 cm/s and ICA/CCA ratio ≥ 2.7</td>
<td>PSV &gt; 250 cm/s or ICA/CCA ratio &gt; 3.2</td>
</tr>
<tr>
<td>50-99%</td>
<td>PSV ≥ 340 cm/s and ICA/CCA ratio ≥ 4.15</td>
<td>PSV &gt; 250 cm/s and ICA/CCA ratio &gt; 3.2</td>
</tr>
</tbody>
</table>

PSV: Peak systolic velocity; EDV: end-diastolic velocity; ICA, internal carotid artery; CCA, common carotid artery.

*PSV and EDV measurements for stented carotid arteries are performed within the stented segments.

GOING BEYOND STENOSIS...
EVALUATING THE CAROTID PLAQUE:

- Identifying patients with less severe stenosis and without symptoms who may benefit from CEA/TSA continues to be a challenge.
- In recent years, evaluation of the carotid plaque in a different manner placing less emphasis on the severity of the stenosis and more emphasis on the morphology and functional characteristics of the plaque.

Carotid Intima-Media Thickness (c-IMT) is defined as the distance between the lumen-intima interface and the media-adventitia interface\(^1\).

Most commonly measured in the CCA on the far wall from B-mode (2D images) with linear US transducers typically using frequencies 7.5-10 MHz\(^2\).

The arterial wall segment should be assessed in a longitudinal view and semi-automated c-IMT measurement (≥ of 10mm length) of the selected segment using an edge detection algorithm.

Following formula has been proposed by Homma et al. for calculating the age-related normal thickness:

\[
(0.009 \times \text{age}) + 0.116
\]
DEFINITION

- Discrete carotid plaques are commonly defined as a focal structure that encroaches into the arterial lumen of at least 50% of the surrounding c-IMT or demonstrates a thickness of $\geq 1.5$ mm as measured from the media-adventitial interface to the intima-lumen interface$^1$.


MORPHOGENESIS OF THE PLAQUE

- Atherogenesis is a chronic multifocal disease of the major arteries characterized by the formation of arterial intimal plaques.
- Lesions consist of accumulation in the intima of intra- and extracellular lipids, cells and associated matrix fibres, as well as regions of necrosis including tissue debris and lipids in various physical states.
- These components tend to be stratified and organized, often in a manner which suggests both healing and recrudescent reactions.
Atherogenesis is a chronic multifocal disease of the major arteries characterized by the formation of arterial intimal plaques. Lesions consist of accumulation in the intima of intra- and extracellular lipids, cells and associated matrix fibres, as well as regions of necrosis including tissue debris and lipids in various physical states. These components tend to be stratified and organized, often in a manner which suggests both healing and recrudescent reactions.

Different classifications of plaque ultrasonic appearance have been proposed in the literature:

- Reilly classified (O’Donnell, 1985) carotid plaques as homogenous and heterogeneous
- Johnson (1985) classified plaques as dense and soft
- Widder (1990), as echolucent and echogenic based on the their overall level of echo patterns
PLAQUE CLASSIFICATIONS

• Gray-Weale (1988) described 4 types, based on echogenicity:
  type 1, predominantly echolucent lesions,
  type 2, echogenic lesions with substantial (>75%) components of echolucency,
  type 3, predominantly echogenic with small area(s) of echolucency occupying <25% of the plaque
  type 4, uniformly dense echogenic lesions.

• Geroulakos (1993) subsequently modified the Gray-Weale classification by using a 50% area cut off point instead of 75% and by adding a fifth type, which as a result of heavy calcification on its surface cannot be correctly classified.

PLAQUE CLASSIFICATIONS

• Supplementing this classification with other important criteria including plaque surface characteristics (Langsfeld, Geroulakos, Lusby, Widder) one can distinguish the following types of plaques on US:
  type I, echogenic and homogenous plaque with a clearly delineated smooth surface
  type II, plaque of mixed echogenicity with predominantly echogenic portions and an irregular surface
  type III, predominantly echolucent or heterogeneous plaque with poorly delineated surface
  type IV, plaque not visualized or suggested only by isolated echogenic spots in an otherwise echolucent lesion. Plaque only indirectly identified as a filling defect on color flow images.
VULNERABILITY OF THE PLAQUE

- Plaque vulnerability seems to be related to the size of the atheromatous core, the thickness of the fibrous cap and inflammation within the cap.
- Therefore, unstable plaques tend to have a thin fibrous cap and a necrotic core situated near the surface.¹
- This may predispose to rupture and exposition of the thrombogenic atheroma to blood flow.²

RISK FACTORS AT THE TISSUE LEVEL

- **Hypercholesterolemia** (lipoprotein fractions present)¹
- **Hypertension** (changes in the thickness & composition of artery walls and affect smooth cell muscle cell metabolism)²
- **Diabetes** (alters lipid metabolism affecting blood lipid levels; smooth cells may also be affected & alter artery wall composition)
- **Smoking** (may cause smooth muscle spasm or contracture)³
- **Sedentary life style**

HEMODYNAMICS AND THE LOCALIZATION OF THE PLAQUE

- The increased susceptibility of certain vessel segments and geometric configurations indicate that mechanical factors associated with flow and with mural tensile stress create local conditions which predispose to plaque formation\(^1,2,3,4,5\).

- Wall shear stress, the frictional force exerted on the endothelium by blood flow has been shown to be clearly related to both atherosclerotic and non-atherosclerotic thickenings\(^6\).  

\[ \text{Inflow side of branches, inner curvature at bends and opposite the flow divider at bifurcations result in reactive intimal cellular reactions and delay clearance of circulating particles from the susceptible regions.} \]

- The area of maximal intimal thickening at the lateral wall of the bulb is the region with flow separation, shear stress reversal and vortex formation.

---

HEMODYNAMICS AND THE LOCALIZATION OF ATHEROSCLEROSIS

- The carotid bifurcation hemodynamics are influenced by the presence of the carotid bulb.
- It is one of the few sites in which the lumen enlarges significantly in the direction of flow.
- At autopsy carotid bifurcations show the greatest intimal thickening and plaque formation at the outer wall of the carotid bulb, beginning at the origin of the vessel from the CCA. Plaques were usually the thickest near the midpoint of the bulb opposite the flow divider.

THE UNSTABLE / VULNERABLE PLAQUE CONCEPT

- It is used to describe plaques that are more prone to local thrombosis and distal embolization leading to stroke.\(^1,2\)
- Morphological features associated with plaque instability include thin fibrous cap, macrophage accumulation, reduced number of matrix producing vascular smooth muscle cells, and large lipid-filled core.\(^1,2\)
- The presence of plaque ulceration, plaque irregularity, or in-situ thrombus on carotid ultrasound may indicate a vulnerable plaque and increases the risk of stroke.\(^3\)

\(^1\). Neurology 2005;65:794-801; \(^2\). Eur J Vasc Endovasc Surg 2008;35:2-8; \(^3\). Stroke 2005;36:2764-2772;
THE UNSTABLE / VULNERABLE PLAQUE CONCEPT

- Histological studies have shown that plaque inflammation and the presence of adventitial vasa vasorum, intimal angiogenesis and plaque neovascularization are strong predictors of instability.

- Plaques with hypoechoic areas consisting of cholesterol, lipid deposits, cell debris and necrotic residuals, showing intraplaque hemorrhage cause a sudden increase in plaque volume and rupture (higher risk of cap thinning and surface endothelium rupture) with subsequent ulceration, distal embolization and stroke\(^1\). 

---

B-MODE EVALUATION

- High-resolution vascular B-mode and Doppler US has been shown to accurately depict a flow limiting stenosis in the carotid arteries\(^1\).

- Multiple US parameters giving an information about plaque characteristics and composition have been investigated.

- Echolucency, heterogeneity, border irregularity have been studied.

---

High-resolution vascular B-mode and Doppler US has been shown to accurately depict a flow limiting stenosis in the carotid arteries. Multiple US parameters giving an information about plaque characteristics and composition have been investigated. Echolucency, heterogeneity, border irregularity have been studied.

Border regularity:

- detection of irregularities in the luminal border of the plaque and of ulceration:
- The European Carotid Plaque Study group used B-mode and found a sensitivity of 47% and a specificity of 63%\(^1\) in the detection of plaque ulcerations.
- Other studies added Doppler techniques to B-mode for the detection of ulcerations and showed, despite a large variance in results, a slight improvement in mean sensitivity 60% (38-94%), and specificity 74% (33-92\%)\(^2-6\).


Another one\(^1\) showed that border irregularities on B-mode US, rather than just ulceration could be detected with a high sensitivity 97% and specificity 81%.
B-MODE EVALUATION

• Some studies\textsuperscript{1,2} compared border regularity with the plaque composition.

• The presence of an irregular border on US was shown to predict an intraplaque hemorrhage with a sensitivity of 81% and a specificity of 85%, while heterogeneity and calcification on US had a poor predictive value for the presence of an ulceration.


B-MODE EVALUATION

Echolucency:

• Numerous studies have shown that echolucent plaques contain significantly higher amounts of “soft” constituents (lipids, intraplaque hemorrhage), while echogenic plaques contain more fibrous tissue and calcifications\textsuperscript{1,2,3-5}.

• Another study showed that examination of echolucency for the detection of plaque components has low sensitivities (34%) and specificities (36%) for the detection of intraplaque hemorrhage and intraplaque hemorrhage with atheromatous debris (sensitivity 51%, specificity 68%)\textsuperscript{6}.

**COMPUTED BASED ANALYSIS**

- To improve the detection of plaque components, quantification of echolucency has been developed by gray-scale median (GSM), pixel distribution analysis, and integrated backscatter analysis.

- The echolucency in the region of interest (ROI) is expressed in a 256 gray-tone range where 0 is black and 255 white.

- Recent studies based on GSM values of the carotid plaque showed that a low GSM value (hypoechoic lesions) was associated with increased risk of CV events (good predictor of plaque behavior).  


**B-MODE EVALUATION**

- A strong correlation was found between the GSM and the amount of fibro-calcified tissue in the plaque.

- However, no correlation was found between the GSM and the lipid core size and only moderate correlations were found between the GSM and other tissue components.

- A plaque mapping system in 3 GSM ranges (<50 =red; 50-80 =yellow; >80 =green) has been developed that may facilitate the detection of the lipid core in the plaque. It showed a sensitivity of 84% and a specificity of 75% for localizing the lipid core.

B-MODE EVALUATION

Heterogeneity

- The division of plaques in homogenous and heterogeneous showed that heterogeneous plaques contain significantly more calcifications, while no difference “soft tissues” was found1,2,3.
- The evaluation of plaque heterogeneity improved sensitivity (76%) and specificity (85%) for the detection of intraplaque hemorrhage over echolucency4.
- The evaluation of plaque heterogeneity predicted fibrous cap thickness and the location of lipid core with sensitivities of 77% and 74% and specificities of 22% and 17% respectively5.

PLAQUE & STENOSIS EVALUATION

- Combined echolucency and heterogeneity scales have been developed and resulted in varying sensitivities ranging from 39% to 94% and specificities ranging from 57-80% for the detection of various components.1,2,3

- In patients with asymptomatic stenosis, the major predictors of the risk for CV events which have been identified:
  - the progression of the carotid lesion,
  - an irregular surface and
  - a non-homogeneous echographic appearance.

Progression of the degree of stenosis was the parameter showing the closest correlation with the development of new neurological symptoms.4


In casadei et al. 2014

The first prospective study to demonstrate a link between stroke and the echogenicity of carotid plaques was conducted by Johnson et al. [4]. Three years of followup data on 297 symptomatic patients showed that TIA or strokes had occurred in 51% of those whose plaques had been hypo or anechoic at baseline, as opposed to only 4.4% whose plaques had appeared hyperechoic. One of the most interesting studies was a multicenter initiative organized by the European Carotid Plaque Study Group. Initially published in July 1995 and republished in September of 2011 [5,6] this study included 270 patients scheduled for carotid endarterectomy in 9 different facilities in Europe. The main findings were as follows: 1) carotid plaque echogenicity on B-mode imaging was inversely correlated with the “soft” material contained in the plaque (p < 0.005), and plaque hyperechogenicity was directly correlated with the presence of calcifications (p < 0.0001)
In casadei et al. 2014

Carotid artery plaque morphology and IMT are expressions of different biological aspects of atherosclerosis with different implications in terms of vascular disease [9]. The IMT is an important predictor of cardiovascular disease, but it displays closer correlation with left ventricular hypertrophy than with atherosclerotic coronary artery disease. Compared with the IMT, carotid plaque morphology and surface area are both better predictors of stroke, myocardial infarction, and cardiovascular death [10-12].

3D-ULTRASOUND EVALUATION

• It has emerged as a new valuable technique for the evaluation of carotid plaques[1]. Conversion into 3D helps overcome the inability of 2D US to evaluate the composition of the entire plaque and allows to measure its volume.

1. Atherosclerosis 2008;198:129-135
• Several studies\textsuperscript{1-7} support the good reproducibility of the 3D US on the evaluation of the carotid plaque volume.

• However further studies are needed to establish if 3D is superior to 2D US in the identification of the vulnerable plaque\textsuperscript{8}.


\textbf{4D-ULTRASOUND EVALUATION}

• It allows assessment of a unique feature of carotid plaques: \textit{Plaque mobility}.

• The dynamic interaction between the carotid plaque and the local hemodynamic environment seems to be related to the vulnerability of the plaque\textsuperscript{1}.

• Plaque surface movement may be related to surface cracking and fissuring which in turn may be related to plaque vulnerability.
In comparison to asymptomatic patients, those with symptomatic carotid stenosis tend to have focal movement disparities on the plaque surface. However, further studies are warranted to determine whether plaque surface motion patterns can identify vulnerable plaques in patients with carotid artery stenosis.

It has been suggested that reduced strain is a feature of "vulnerable" plaques. Moreover, vulnerable plaques display an outer remodeling, a feature which is strongly associated with reduced strain. Vulnerable plaques are more frequent in patients with hypertension, dyslipidemia and diabetes, in whom reduced strain was more frequently observed. It has been also shown that increased carotid stiffness seems to be important in the pathophysiology of cerebrovascular disease.

MECHANICAL PARAMETERS OF THE PLAQUE

- It has been suggested that reduced strain is a feature of “vulnerable” plaques\(^1,2\).

- Moreover, vulnerable plaques display an outer remodeling, a feature which is strongly associated with reduced strain\(^3,4\).

- Vulnerable plaques are more frequent in patients with hypertension, dyslipidemia and diabetes, in whom reduced strain was more frequently observed\(^3,4\).

- It has been also shown that increased carotid stiffness seems to be important in the pathophysiology of cerebrovascular disease\(^5\).

MECHANICAL PARAMETERS OF THE PLAQUE

- Echotracking allows the assessment of local arterial stiffness deriving the pressure–diameter curve of the artery (the measurements of stroke changes in diameter and local PP should be determined simultaneously) and calculating the local PWV from the time delay between the two adjacent distension waveforms.

- In addition, it provides information about the presence of plaques and precise measurement of intima-media thickness.
MECHANICAL PARAMETERS OF THE PLAQUE

- Echotracking is particularly well suited to determine the mechanics of the arterial wall and at the site of atherosclerotic plaque and in its vicinity
- High resolution multiarray echotracking is using bidimensional acquisition mode images. It allows the analysis of arterial wall motion, distensibility and stiffness.

![Image of echotracking](image)

CONTRAST ENHANCED ULTRASOUND (CEUS)

- The clinical applications of CEUS for vascular use include:
- Enhancement of the carotid artery lumen, which results in improved visualization of luminal irregularities including soft plaques, dissections and ulcerations

A variety of ultrasound contrast agents have been used for visualization of the intraplaque microvascularization (VV imaging) (Optison, Definity, SonoVue).

They consist of gas-filled MB which are small enough (1-5 µm) to pass through the capillary system. They are routinely injected via a peripheral vein as a bolus, followed by a saline flush.

J Am Coll Cardiol Img 2010;3:761-771
A variety of ultrasound contrast agents have been used for visualization of the intraplaque microvascularization (VV imaging) (Optison, Definity, SonoVue).

They consist of gas-filled MB which are small enough (1-5 µm) to pass through the capillary system. They are routinely injected via a peripheral vein as a bolus, followed by a saline flush.

J Am Coll Cardiol Img 2010;3:761-771
A variety of ultrasound contrast agents have been used for visualization of the intraplaque microvascularization (VV imaging) (Optison, Definity, SonoVue). They consist of gas-filled MB which are small enough (1-5 µm) to pass through the capillary system. They are routinely injected via a peripheral vein as a bolus, followed by a saline flush. Moreover CEUS techniques provide superior enhancement of the proximal walls, leading to improved efficiency and precision of measurements of c-IMT.

Based on the knowledge that acoustically reflective microspheres serve as ideal intravascular tracers, real-time, microvascular assessment of the spatial and temporal heterogeneity of adventitial and intraplaque vasa vasorum (VV) was revealed. Direct visualization of adventitial VV and intraplaque angiogenesis was revealed.

**CONTRAST ENHANCED ULTRASOUND (CEUS)**

- CEUS can visualize vasa vasorum (VV) in the adventitial layer as well as intraplaque neovascularization\(^1\)-\(^6\).

- These microvascular networks are thought to play a central role in the early process of plaque progression and vulnerability and may also be involved in plaque inflammation\(^7\)-\(^8\).


**METHODOLOGICAL LIMITATIONS**

- In the case of calcified plaque, substantial shadowing may occur distal to the plaque, thus hampering plaque and flow evaluation.

- Improvements regarding automated 3D examinations have been made\(^1\)-\(^2\). However, the technical complexity is such that routine application has not yet been accomplished.

- In CH, mainly the sulphur-hexafluoride dispersion called SonoVue\(^\text{®}\) is currently used for CEUS. Side effects such as paresthesia at the site of application and headache after injection (<2%) have been described.

CEUS can visualize vasa vasorum (VV) in the adventitial layer as well as intraplaque neovascularization. These microvascular networks are thought to play a central role in the early process of plaque progression and vulnerability and may also be involved in plaque inflammation.


In the case of calcified plaque, substantial shadowing may occur distal to the plaque, thus hampering plaque and flow evaluation. Improvements regarding automated 3D examinations have been made. However, the technical complexity is such that routine application has not yet been accomplished.

In CH, mainly the sulphur-hexafluoride dispersion called SonoVue® is currently used for CEUS. Side effects such as paresthesia at the site of application and headache after injection (<2%) have been described.

Further development of B-mode imaging as well as the CEUS assessment of the plaque morphology has a big potential not only for the risk stratification of carotid plaques but also for the follow-up of the effects of plaque stabilizing drug therapy.

Another challenging aspect is ultrasonic molecular imaging. For example, highly specific ligands “targeted molecules” (such as monoclonal AB, glycoproteins or peptides) are attached to the shell. The targeted contrast agent can bind to the appropriate target structure. Specifically bound MB remain detectable at the site of the targeted structure.

Very promising results have demonstrated successful in vitro targeted imaging of human clots with abciximab immunobubbles.

1. Stroke 2007;5:1508-1514
**POSSIBLE FUTURE APPLICATIONS**

- Future developments could generate additional targeted MB for the detection of inflammation or angiogenesis.

- Another possible future application is the binding of therapeutic agents, e.g. thrombolytics to MB which could then be released by insonification at the site of vascular obstruction (US mediated drug delivery).

**CONCLUSIONS**

- It is not sufficient to assess the risk of stroke of a carotid plaque solely based on the degree of stenosis and the presence of neurological symptoms.

- It has become clear after the Asymptomatic Carotid Surgery Trial (ACST), that there is a need to identify a subgroup of patients with asymptomatic carotid plaques who would benefit from ttt of their carotid stenosis¹.
CONCLUSIONS

• Ultrasound is a noninvasive screening imaging tool which allows safe and reliable information for early detection of surrogate markers of atherosclerosis.

• CEUS appears to be an emerging technique serving as a valuable method for the early detection of premature atherosclerosis and for the detection of vulnerable plaques in at-risk populations.

• It therefore could help to identify individuals exhibiting an unstable or vulnerable plaque.

• If “plaques at risk” could be reliably identified the therapeutic decisions for either medical or surgical / endovascular treatment could be made more rationally.
Ultrasound is a noninvasive screening imaging tool which allows safe and reliable information for early detection of surrogate markers of atherosclerosis.

CEUS appears to be an emerging technique serving as a valuable method for the early detection of premature atherosclerosis and for the detection of vulnerable plaques in at-risk populations.

It therefore could help to identify individuals exhibiting an unstable or vulnerable plaque.

If “plaques at risk” could be reliably identified the therapeutic decisions for either medical or surgical / endovascular treatment could be made more rationally.

European Society of Neurosonology and Cerebral Hemodynamics