Angioplasty and Stenting of the Carotid and Supra-Aortic Trunks

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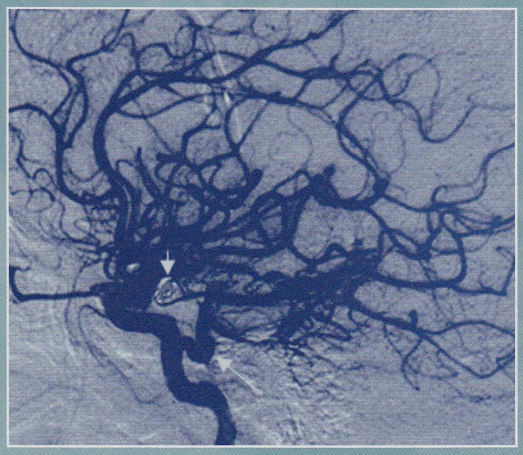

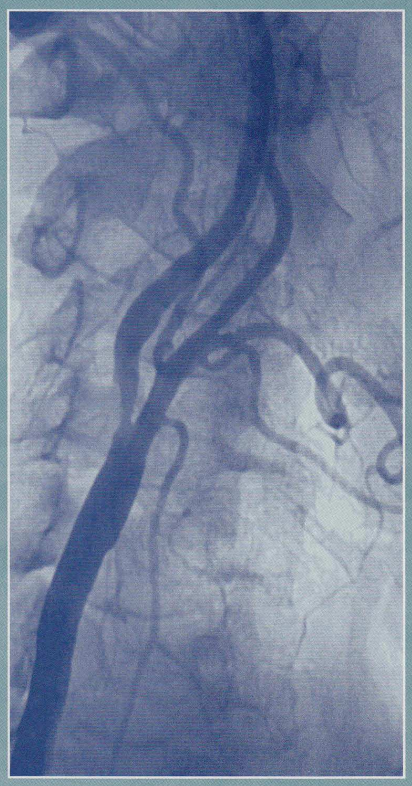

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Importance of carotid plaque characterization before carotid angioplasty and stenting: The ICAROS Study

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Introduction

Stroke is one of the leading causes of death in the USA. Carotid endarterectomy (CEA) is the gold standard treatment to reduce stroke in symptomatic and asymptomatic patients with significant carotid stenosis, as demonstrated in multicentre randomized trials.[1,2]

Carotid angioplasty and stenting (CAS) has recently emerged as an alternative to CEA;[3–5] however, the use of balloon angioplasty and stenting in this anatomical site has been limited, owing to the availability of excellent surgical therapy and concern regarding embolic stroke. Cerebral embolization is the most devastating complication of CAS.[6]

To reduce the risk of embolic lesions in the brain, i.e. transient ischaemic attack (TIA) or stroke, the best technique for CAS should be applied perioperatively, with correct use of guidewires, catheters, balloons, stents and protection devices, according to the anatomical and clinical characteristics of each patient. This is necessary, but not sufficient to achieve the best results. The preoperative identification of patients with different embolic risk, having plaques with different morphological characteristics, can also be beneficial in reducing neurological complications.

Embolic risk with carotid artery stenting

The embolic risk during CAS is well documented. Ohki et al.[7] developed an *ex vivo* human model to study the embolic potential of carotid bifurcation angioplasty and stenting. In these experiments endarterectomy specimens were removed as casts of carotid bifurcation, which were encased in a polytetrafluoroethylene (ePTFE) wrap, to re-create the adventitia. Balloon angioplasty with stenting was then performed, and the effluent from each specimen was filtered for embolic particles larger than 120 μm. The embolic risk of balloon angioplasty was correlated to plaque characteristics (according to Gray-Weale/Geroulakos classification) and the severity of stenosis (calculated from *ex vivo* angiography). It is important to note that embolic particles were obtained in each case and that the number varied substantially among specimens (range 2–126); moreover, these particles were predominantly composed of atherosclerotic debris and some organized thrombus and calcified material. The mean size of the particles was 338 μm and the range was 120–2100 μm. This study clearly showed that echolucent plaques ($p = 0.012$) and plaques with stenosis of 90% or more ($p = 0.04$) generated a higher number of embolic particles after balloon angioplasty and stenting. Multiple regression analysis revealed that echogenicity and severity of stenosis were significant independent risk factors.

Coggia et al.[8] developed an *ex vivo* model using fresh carotid bifurcations, explanted during carotid bypass graftings, to analyse quantitatively the embolic particles generated at each stage of the angioplasty procedure. Carotid angioplasty was performed on the non-endarterectomized carotid bifurcation; the excised arterial specimen included the distal 5 cm of the common carotid artery (CCA), the proximal 3 cm of the internal carotid artery (ICA) and 1 cm of the external carotid artery (ECA). This model was used to assess the

number of particles and their size, and the subsequent risk of stroke before the procedure, after the lesion was crossed with a guidewire, after the placement of the balloon catheter and after balloon angioplasty. The study showed that:

- carotid angioplasty generates embolic particles after each stage of the procedure;
- the size of most embolic particles generated was less than 60 μm, with many platelet or cholesterol microthrombi. These very small particles could be trapped in the cerebral capillaries with infraclinical consequences. However, the progressive neuropsychic sequelae of such microemboli are unknown;
- the maximal size of particles (detected in the last phase, i.e. during the balloon angioplasty) was between 1000 and 1500 μm. The neurological risk of particles measuring more than 1000 is certainly high because they can occlude cerebral arteries and communicating branches of the circle of Willis. These large particles were scarce, but a single embolus of that size could induce a stroke.

Primary crossing of the carotid plaque with the device carrying the stent remains necessary, with a risk of parietal trauma, especially with irregular or tight stenosis. The selection of patients for carotid angioplasty is therefore crucial.

Histological studies have confirmed that echolucent plaques are predominantly composed of atheromatous debris, lipids and intraplaque haemorrhage, whereas echogenic plaques mainly consist of more stable fibrous tissue.[9–12] Plaques with echolucent areas are more unstable and prone to fragmentation and embolization than are echogenic plaques. If patients with echolucent plaques are excluded from CAS, it may be possible to reduce the risk of stroke further, and to maximize the potential of balloon angioplasty and stenting for the management of stenosis of the carotid bifurcation.

Effect of embolic particles on the brain

Several studies have analysed the impact of released particles during CAS on the brain.

Using transcranial Doppler ultrasound, Ackerstaff et al.[13] studied the effect of the total number of particles detected during CEA on perioperative neurological events. It was shown that microemboli (> 10) noticed during the procedure were related to both intraoperative ($p < 0.002$) and postoperative ($p < 0.02$) cerebral implications. Microemboli that occurred during shunting were also related to intraoperative complications ($p < 0.007$). An isolated microembolism never resulted in new morphological changes on postoperative cerebral computed tomographic (CT) scans. In contrast, the detection of more than 10 microemboli was significantly ($p < 0.005$) related to new lesions on magnetic resonance scans. This study clearly showed the importance of the number of embolic particles in the occurrence of perioperative stroke.

Rapp et al.[14] performed *ex vivo* angioplasty on 20 human carotid plaques removed *en bloc*. Plaques were placed within PTFE grafts, then angioplasty was performed (guidewire insertion, angioplasty and stent delivery). After each procedure, the lumen was flushed, effluent was collected and fragments were counted. Rats were then injected with saline or solution with different fragments (< 200 μm, 200–500 μm). The animals were killed at 1, 3 and 7 days, and brain sections were examined for cell viability. The following conclusions were reached.

- Every manoeuvre performed released atherosclerotic debris.
- The brain appears to have an impressive tolerance to microemboli.
- Patients with more frequent emboli may have a higher rate of stroke.
- Large fragments may cause acute neurological complications.
- Even small particles may cause neuronal ischaemia at later time points, with subtle neurological dysfunction in late follow-up.

Reduction of the embolic burden on the brain

This can be achieved in several ways.

1. Correct CAS technique is important.
2. Protection devices, such as occlusive balloons and filter devices may be used. Several brain protection devices have been proposed and adopted, and in some cases very promising results have been reported. Theron in 1990 suggested the use of a triple coaxial catheter with a distal occluding balloon in the distal ICA, reporting better results than in non-protected procedures.[15,16] Kachel routinely uses a proximal occluding balloon in the CCA, with good results.[17] The criticism regarding proximal occlusion is that frequently the backflow from the ECA may determine an anterograde flow in the ICA, and not the opposite. This could maintain the risk of embolization during angioplasty even with a proximal occlusion. Some authors have therefore suggested using occluding balloons in both the CCA and the ICA, such as Parodi's protection device.[18] PercuSurge proposed a refinement of the distal occluding balloon, included in the same wire, so that the angioplasty balloon may be advanced over that wire without danger of mobilizing debris and

embolization, and this has been successfully adopted.[19] Other devices designed for the ablation of embolic particles use retractable filters, such as that used by Roubin and co-workers.[20] Nevertheless, it should be noted that whatever brain protection device is used, protection is not provided throughout the entire procedure.

3. Patients can be selected preoperatively, according to the echographic pattern of the plaque.

Echographic evaluation of the plaque

The study of plaques began in the 1960s, when surgeons could only see directly the type of the plaque, i.e. haemorrhagic or ulcerated, calcified or fibrolipidic. Angiography was performed to calculate the grade of stenosis and to search for ulceration in the plaque. The plaques were then analysed with microscopic devices, to detect intraplaque haemorrhage or microscopic ulceration. Several studies tried to find a correlation between the characteristics of the plaque and the presence or absence of neurological symptoms or cerebral CT lesions, sometimes with different results.

In the 1980s surgeons had a new instrument to study the plaque preoperatively, using the duplex scan. The reliability of duplex scan ultrasonography in identifying plaque structure and composition has been widely studied in the past few years, with variable results.[11,21–26] However, the advent of high-resolution B-mode scanners has improved histological and clinical correlation for plaque characterization, increasing the likelihood that duplex scanning can serve as a non-invasive screening tool to classify more accurately potential candidates for CAS, according to lesion severity and morphology. The ability of modern duplex to measure carotid luminal stenosis accurately has been well documented.[27] Moreover, investigators have suggested that plaque echogenicity may be a useful indicator of embolic potential in the carotid arteries.[11,28–30]

The study of carotid plaque morphology on ultrasonography has relied on visual characterization, based on subjective and qualitative evaluation of the B-mode images. This has created controversy concerning the role of some histological characteristics of the plaque seen on the duplex scan, i.e. the ulceration or the intraplaque haemorrhage, and their correlation with the presence or absence of neurological symptoms.[23–26,31–35] As consequence of this, Greenhalgh recently wrote: '... the fact that it has taken so long for plaque type to be shown to relate to stroke risk in asymptomatic severely stenosed carotid artery, can mean one of two things: It can mean a plaque type never has and never will, relate to stroke risk—and second, that the precise combination of findings has not been clearly recognized.'[36] Moreover, even though it is generally accepted that the composition and the characteristics of the plaque may influence the outcome of CEA and CAS, especially in the case of CAS where the plaque is not removed but remodelled, indication to either one of the two procedures is mostly based, both in trial and in clinical practice, on the percentage of stenosis and the presence or absence of preprocedural neurological symptoms, while the features of the plaque are somehow disregarded and ignored.[1,2] The reason for this is related to the fact that the percentage of stenosis, as well as the presence or absence of symptoms, are easy to identify and quantify, whereas the plaque is usually defined as soft, lipidic, fibrolipidic, haemorrhagic, colliquated, ulcerated, fairly homogeneous, and so on, which makes the parameter rather unspecific and unreliable.

To overcome the unreliability related to the morphological characteristics of carotid plaques, one should keep in mind that echography means 'detection of echoes', i.e. detection of echogenicity. Echography can reliably register areas with a lot of echoes (hyperechoic or echogenic) and areas with few echoes (hypoechoic or echolucent). Other characteristics of the plaque, such as the ulceration or haemorrhage, are subjective interpretations, prone to creating confusion and doubt. Carr et al.[24] found both significant and non-significant correlation between neurological symptoms and lesions, and the presence of ulceration and haemorrhage, using different definitions of ulceration and haemorrhage.

Only objective and quantitative grading of plaque echogenicity using computerized measurements provides an operator-independent assessment of plaque echoic structure, which could prove more accurate than visual characterization. The grey-scale median (GSM) was created based on these assumptions.

Grey-scale median

The GSM is a computer-assisted grading of the echogenicity of carotid plaques. It is a measure of the overall plaque echogenicity, which is a quantitative index of the echoes registered from the plaque.

The following conditions are needed to ensure the reliability of the GSM.

- The duplex scanner must be regulated following standard settings. B-mode scan settings are adjusted using the postprocessing button so that the maximum dynamic range is used with a linear postprocessing curve. The frame rate, i.e. the number of scans performed by the probe producing the images, must be positioned at the maximum level, while persistence is set at a medium to low level. The persistence is displayed on-screen as a series of numbers from 1 to 5 and the correct persistence would be 2 or 3. The time gain compensation (TGC) curve is adjusted (gently sloping) using the buttons

provided on the duplex device to produce a uniform intensity of echoes on the screen, with the aim of obtaining images where the far and near wall of the artery produce the same echogenicity. The overall gain is eventually increased until the appearance of the plaque is judged to be optimal and noise appears within the lumen. It is then decreased so that at least some areas in the lumen appear to be free of noise.

- Scan and printer settings should not be altered during the examination.

GSM is calculated in the following manner.

1. The colour information (Fig. 15.1) in the image is omitted so that all the processing and analysis is performed on images in grey mode (Fig. 15.2). The coloured images are used for reference, which helps to outline echolucent plaques.

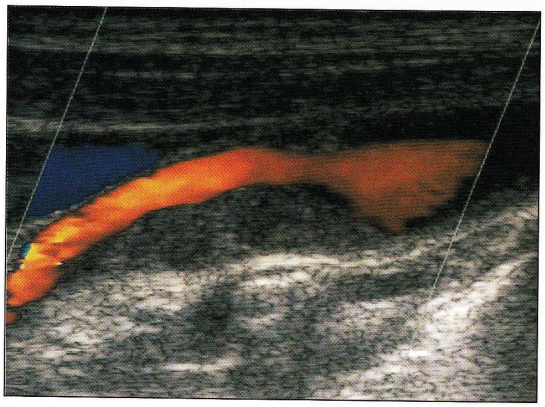

Figure 15.1
Colour image of the plaque.

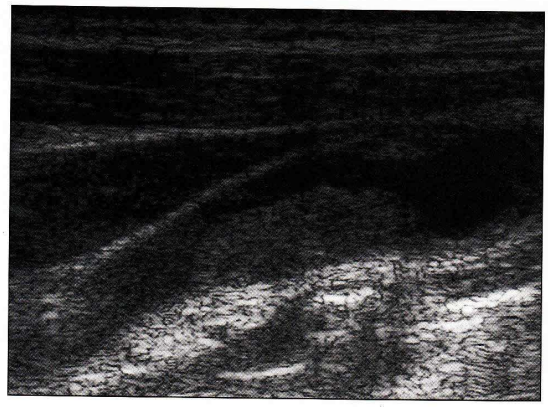

Figure 15.2
Colour function should be omitted in duplex scanner and the grey mode image should be saved as a digital file.

2. An area in the blood (free of noise) is selected. Using the histogram facility in the program, the median value of the grey levels of all pixels (the GSM) is obtained (Fig. 15.3).
3. Similarly, part of the adventitia is selected. Measurements of the GSM are made at the brightest part of the adventitia on the same arterial wall as the plaque (Fig. 15.4).

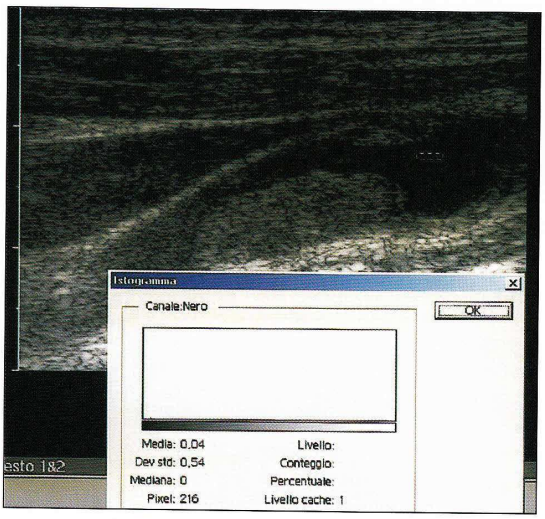

Figure 15.3
In Adobe Photoshop select an area in the blood with the function 'lasso', then in the 'image' menu, select the 'histogram' function, checking that the median (GSM) is between 0 and 5. If not, the duplex scan is not set properly.

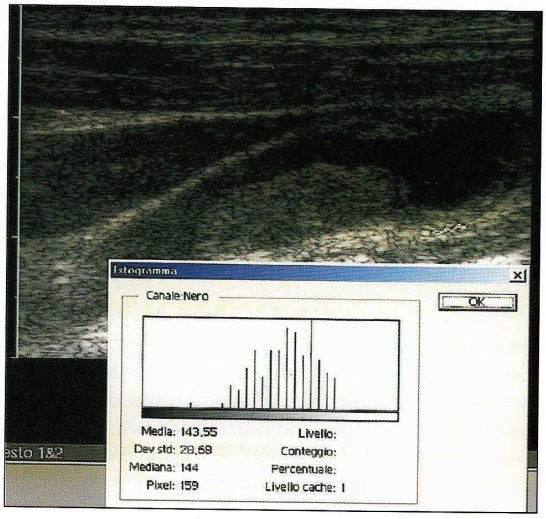

Figure 15.4
Select an area in the brightest point of the adventitia (every value is OK) then in the 'image' menu, select the 'histogram' function and register the median (GSM).

4. The image is standardized. Algebraic scaling of the whole image is performed using the 'curves' facility of the software. This is linear and based on two reference points: blood and adventitia. The scale is adjusted so that the grey value of the blood is in the region of 0–5 and that of the adventitia in the region of 185–195 (Fig. 15.5). Thus, the grey values of all pixels would change as defined by this new linear scale (Fig. 15.6). The reproducibility of this method (with four observers, two duplex scanners and 23 carotid images) has been found to be: coefficient of variation (CV) 0.047; reliability coefficient 0.99.
5. The echodensity of grey levels of pixels in the plaque is measured. In standardized images plaques are outlined using a mouse of a personal computer (Fig. 15.7) and the following measurement is obtained from the histogram of the grey shades of plaque pixels. GSM: defined as the median of overall grey shades of the pixels in the plaque (Fig. 15.8).

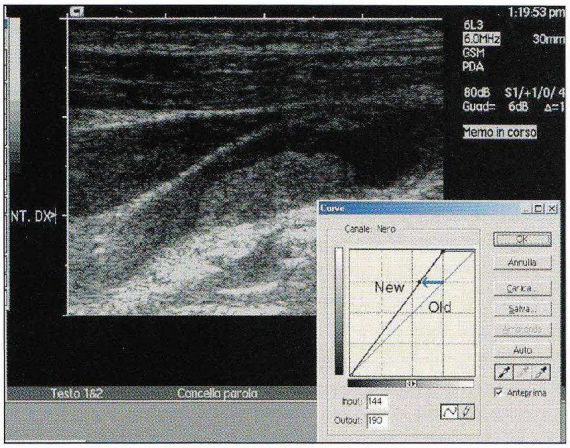

Figure 15.5
Standardization. In the 'image' menu, select the 'rule' function, then 'curve' the function. Modify the curve so that the new linear curve has the input value of the GSM of the adventitia in the point with the output value of 190.

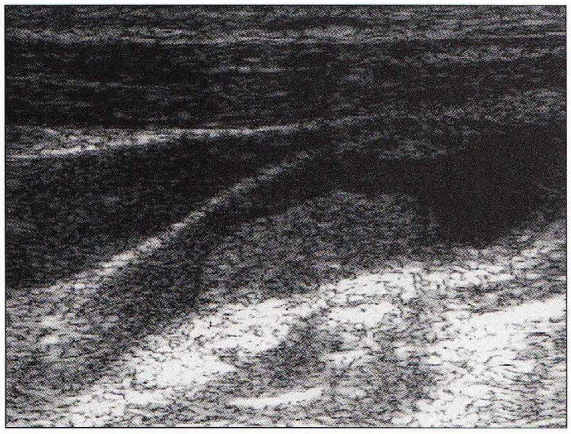

Figure 15.6
Standardized image.

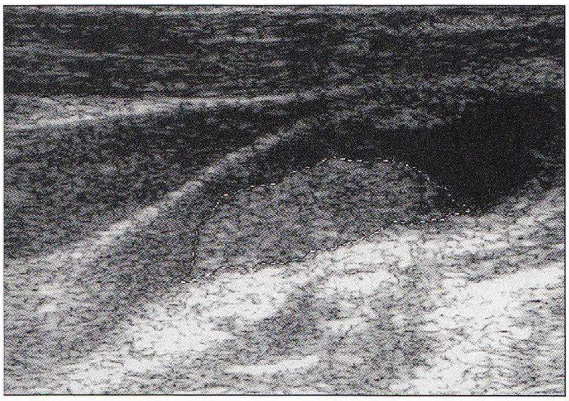

Figure 15.7
Outlining of the plaque.

It has been demonstrated that: [37–44]

- the GSM of plaques associated with negative CT scans is lower than that of plaques associated with positive scans ($p < 0.0001$)
- the GSM of symptomatic plaques is lower than that of asymptomatic plaques ($p = 0.002$)
- a near-perfect agreement was obtained between GSM of plaques from images on video and magneto-optical disk. The CV among four observers was 4.7% after image standardization of the plaque. Images from different scanners, taken by different ultrasonographers and through different peripherals, can be standardized so that measurements of plaque echodensity become comparable.

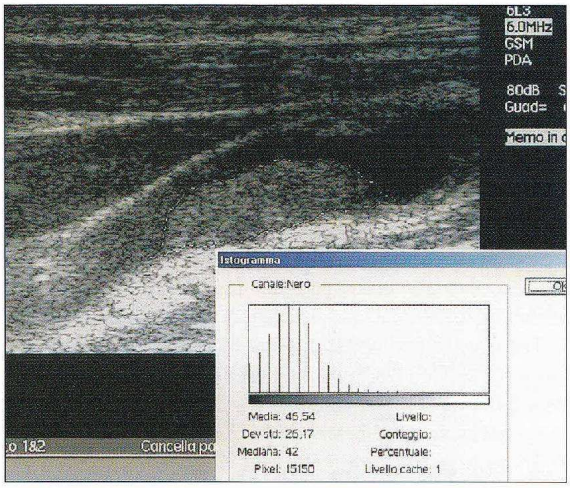

Figure 15.8
Calculation of the GSM in the standardized plaque.

ICAROS study

Summary

ICAROS (Imaging in Carotid Angioplasty and Risk of Stroke) is a registry of carotid angioplasties, which reports any cerebral event following the procedure and correlates the risk of cerebral embolization with the echographic characteristics of the carotid plaque.

The aim of ICAROS is to determine the preintervention criteria that can identify the echographic features of the carotid plaque at risk of stroke and those at low risk of stroke during angioplasty, so that a better selection for angioplasty and stenting can be made.

Rationale

Endovascular angioplasty in coronary, renal and aortoiliac vessels represents a well-established method of treatment and the respective indications for angioplasty, surgery or medical therapy are fairly well defined in these areas. This is not the case for the endovascular treatment of extracranial carotid arteries, which is still controversial. Despite the fact that many surgeons remain opposed to angioplasty of the carotid arteries, this new therapeutic option is increasingly being adopted.[3–5]

CEA surgical procedures have been refined over the past 40 years, with a steady improvement in the results; through appropriate indication, a cumulative morbidity and mortality rate below 3% has been achieved in most centres.[1,2] Any alternative therapeutic option has at least to match this standard.[45]

While in early reports angioplasty of carotid vessels had an unacceptably high complication rate, with the refinement of techniques and devices, morbidity and mortality rates have been reduced in most recent endovascular experiences.[3–5]

It is difficult to compare the results of endovascular treatment of carotid stenosis with those of conventional surgery, mostly because of different inclusion criteria adopted in different reports and also because of the short follow-up usually available for angioplasty. Hence the need for a controlled randomized clinical trial, with the aim of comparing the effectiveness and safety of angioplasty and stenting, versus CEA.[46,47]

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) trial[48] was begun to determine the risks and benefits of carotid and vertebral angioplasty and to compare them with surgical or best medical treatment.

Three large trials are now being organized specifically for carotid disease: the Carotid Revascularization Endarterectomy versus Stent Trial (CREST),[49] the Carotid Artery Stenting versus Endarterectomy Trial (CASET)[50] and the Carotid Revascularization with Endarterectomy or Stenting Systems (CARESS).[51]

Only after these controlled prospective randomized trials have collected enough data, may the indications and the respective role of the different treatment modalities in stroke prevention be defined. To resolve this difficult issue, after the enrolling phases of the trials, a long follow-up from 5 to 10 years will be necessary to obtain the answers. Inclusion–exclusion criteria for these trials consider the percentage of carotid stenosis and the presence or absence of neurological symptoms, but do not give adequate importance to another relevant factor, the morphology of the carotid plaque.

The different morphological characteristics of the lesion are often determining factors in the indication to perform the angioplastic procedure. Heavily calcified plaque contraindicates the endovascular approach, as do more complex bifurcation lesions with friable atherosclerotic material.[52] In contrast, smooth fibrous lesions such as recurrent stenosis following endarterectomy are very responsive to angioplasty and stenting and have low embolic potential.[3,53] It therefore seems meaningful to say that there are 'safe' and 'dangerous' plaques for carotid balloon angioplasty (Fig. 15.9).

Insufficient results are reported in the current literature on the endovascular treatment of carotid stenosis and they cannot give reliable criteria to evaluate which carotid lesions are at different risk of embolization during percutaneous transluminal angioplasty (PTA).[53–56] Nevertheless, the importance of the morphological features of the plaque related to the outcome after carotid angioplasty is increasingly being recognized.[56–58]

In a recent experimental study, using an *ex vivo* human CAS model to correlate the embolic risk with the lesion characteristics, echolucent plaques resulted in a significantly higher number of embolic particles.[7] Similar conclusions were drawn by several studies performed on the morphological characteristics of the carotid plaque, in order to assess the risk of cerebral ischaemia. A diagnostic method, based on a computerized elaboration of the echographic image of the carotid plaque, was used to define a correlation between the echogenicity of the plaque and previous strokes, as diagnosed by brain CT scans.[37–44] This method, as refined by Nicolaides, is being used in a prospective trial on asymptomatic carotid stenosis to assess the risk of stroke (ACSRS).[41] The application of such a computerized method on candidates for carotid PTA, compared with the outcome after the procedure, could give a correlation between the echogenicity of the plaque and the risk of embolization after balloon angioplasty.

Several methods of cerebral protection during carotid angioplasty have been proposed to lower the embolic risk. Whatever kind of cerebral protection is adopted, it may make the procedure safer and give the opportunity to analyse the aspirated and filtered embolic particles for dimension, number and composition. The filtered particles are correlated with the echographic characterization of the plaque, using the comput-

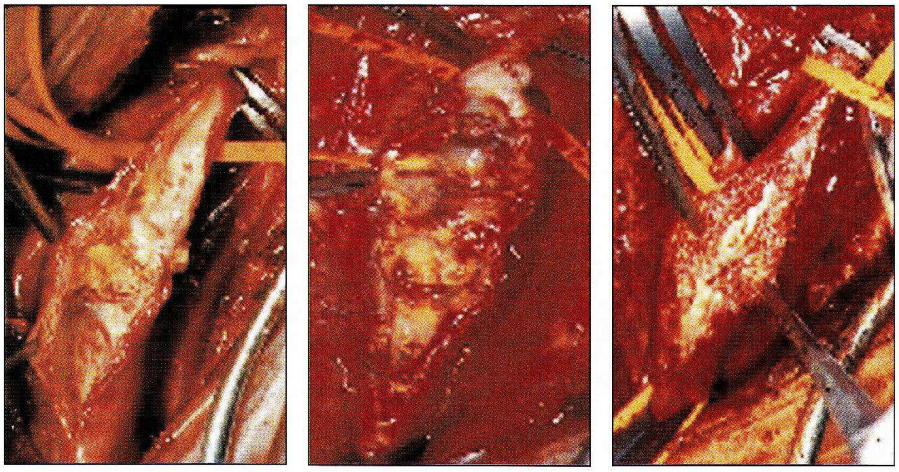

Figure 15.9
Intraoperative images of three different plaques (haemorrhagic, ulcerated and fibrous) from three different patients with symptomatic carotid stenosis of similar rate. The discriminating factors in these three patients for the indications for any procedure should be based on neither the presence or absence of neurological symptoms, nor the percentage of stenosis, but rather the characteristics of the plaque.

erized method, giving the potential risk of fragmentation of the different kinds of plaque that can be prevented by cerebral protection, but may remain after the procedure, causing delayed cerebral suffering. Therefore, such 'cerebral protected' angioplasties may also be extremely useful for ICAROS.

If the criteria are shown to be reliable in assessing the risk of embolism on a controlled series of carotid lesions treated by endovascular angioplasty, a safer diagnostic procedure will be available to indicate suitability for carotid angioplasty and stenting. Moreover, the computerized study of the carotid echography, validated in such a way, would represent an essential parameter to select groups of patients at similar risk of cerebral ischaemia more accurately than percentage of stenosis, thus allowing a proper comparison to be made between endovascular and conventional surgical treatment of carotid lesions, for the prevention of cerebral ischaemia.[59]

Final results

From July 2000 to December 2001, 496 cases were reported from 12 different centres worldwide. In total, 418 patients were entered in this study, while 78 were excluded because of low-quality images, and incomplete information on data forms.

There were 297 male and 121 female patients (Table 15.1). The underlying pathology was restenosis in 227 cases (54.3%) and a primary lesion in 191 cases (45.7%). A stenting procedure was performed in 415 cases (99.3%). A brain protection device was applied in 219 cases (52.4%) (Table 15.2).

The overall number of neurological complications totalled 28 (6.6%): 13 TIAs (3.1%), nine minor strokes (2.1%) and six major strokes (1.4%). Five of the 13 TIAs, three of the seven minor strokes and two of the six major strokes occurred during the course of brain-protected procedures (Table 15.3). Twenty of the 28 complications (71.4%) occurred in

Table 15.1 ICAROS Study: subject characteristics.

• 418 patients:	
– 297 males (71.1%)	
– 121 females (28.9%)	
• Age (years):	
– Minimum: 47	
– Maximum: 83	
Mean: 68.2	

Table 15.2 ICAROS Study: final results.

• Stent	415 (99.3%)
– Carotid Wallstent	372 (89.8%)
– Palmaz	8 (1.9%)
– X-Act Medtnova	23 (5.5%)
– Smart Stent	12 (2.8%)
• Cerebral protection	219 (52.4%)

Table 15.3 ICAROS Study: complications.

• *Overall complications*	28 (6.6%)
• Transient ischaemic attacks	13 (3.1%)
– with brain protection	5
– without brain protection	8
• Minor stroke	9 (2.1%)
– with brain protection	3
– without brain protection	6
• Major stroke	6 (1.4%)
– with brain protection	2
– without brain protection	4

Table 15.4 Relationship between GSM value and neurological complications.

ICAROS Study

	Neurological complications
• GSM < 25	20/155 (12.9 %)
• GSM > 25	8/263 (3.0 %)
	P<0.001

Table 15.5 Conclusions.

ICAROS Study

	Carotid stenting	*Brain protection*
• GSM < 25	High risk	Contraindicated
• GSM > 25	Low risk	Indicated

cases with a GSM < 25 (very soft, echolucent plaques), six (21.4%) with a GSM between 25 and 50, and two (7.2%) with a GSM > 50 (Table 15.4). Out of the total of 418 cases observed, the incidence of GSM < 25 was 37.1%, GSM < 50% was 9.3% and the majority of cases had a 25 < GSM < 50 (53.6%).

On the basis of the data from the ICAROS study, the following conclusions were drawn (Table 15.5).

- CAS should be contraindicated when the preprocedural GSM is less than 25.
- CAS could safely be performed with the mandatory application of a capturing device with a GSM of between 25 and 50.
- Finally, CAS could also be indicated when GSM is over 50. Nevertheless, in these cases, the application of a brain-protection device may be optional or even contraindicated.

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