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Chapter 3

Carotid Artery – Pathology, Plaque Structure – Relationship between Histological Assessment, Color Doppler Ultrasonography and Magnetic Resonance Imaging – Dolichoarteriopathies – Barorreceptors

Ricardo Luis Beigelman, Andrés María Izaguirre,
Francisco Azzato and José Milei

Additional information is available at the end of the chapter

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1. Introduction

Carotid artery atherosclerosis is a major cause of disabling stroke and death [1] and it is thought to be the predominant etiology of stroke in Western society [2]. Moreover, stroke is the third leading cause of death and the primary cause of disability in the world [2].

Compared with medical therapy, surgical endarterectomy or carotid stenting have been proven to decrease stroke in symptomatic patients with severe stenosis[3-7] and in a very selective group of asymptomatic patients suffering of this pathology[8-9]

Nevertheless, clinical assessment of stroke risk had not progressed beyond the use of luminal stenosis in spite of evidence to suggest that this is an inadequate predictor of stroke. [10]

More recently, imaging studies have suggested plaque composition as an independent risk factor for ischemic stroke. [11]

Because of this, many efforts have been made to correlate symptoms and cerebral events with histological studies, color doppler ultrasonography (CDU) and magnetic resonance imaging (MRI).

Carotid dolichoarteriopathies were have also been proposed as a source of cerebral vascular insufficiency but this issue remains very controversial in the literature.[12-14]. In this chapter, our experience on CDU of neck vessels in 885 individuals with carotid dolichoarteriopathies

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(age 1-day-old infants to 90-year-old adults),[15-16], the correlation of plaque appearance between B ultrasonography and pathology, [17] and the histological assessment in 281 carotid endarterectomy specimens [18] will be widely described and discussed.

In this connection, in a pioneer study we made a complete immunohistochemical characterization in complicated carotid plaques. [18] The cellular components of carotid endarterectomy specimens were analyzed to assess their role in the pathogenesis of plaque rupture and intraplaque hemorrhage without rupture. The site of plaque rupture is associated with the presence of an extensive infiltrate of macrophages, T-lymphocytes, scarce B-lymphocytes, mast cells, and smooth muscle cells. Both the plaques showing these features and those with large amounts of lipid and thin fibrous caps, should be considered as "plaques at risk". Intraplaque hemorrhages without plaque rupture may be caused by the breakdown of neoformed vessels in the core, base, and periphery of the plaques. [18]

This paper emphasized the importance of the detection of vulnerable plaque for preventing future cerebral events. The main factors in advanced plaque that are most likely to lead to complications are the thickness of the fibrous cap, the size of the necrotic core and intraplaque hemorrhage, and the extent of inflammatory activity within the plaque.

Later on, we analyzed the relation between the anatomy of the carotid plaques and the presence of symptoms in 281 carotid endarterectomy specimens. [19] Almost 70% of plaque specimens demonstrated thrombus, intraplaque hemorrhage, or both. Thrombosis was observed in one fourth of specimens, and intraplaque hemorrhage in almost two thirds of specimens. Sixty four percent of plaques demonstrated neovascularization. In spite of findings in some published articles, [20] it was not possible to demonstrate that complicated plaques (plaque rupture, thrombosis, intraplaque hemorrhage) are associated with symptoms, and it appears that complicated plaques may occur at any time, irrespective of symptoms. [19]

Regarding the biology of the unstable atherosclerotic carotid plaque, an expression of c-fos, p53 and PCNA was demonstrated by us. [21]

On the other hand, MRI has excellent soft tissue contrast and is able to quantify carotid plaque size and composition with good accuracy and reproducibility and provides an opportunity to prospectively examine the relationship between plaque features and subsequent cerebrovascular events. [22] In a paper by Takaya et al [23] 154 patients with an asymptomatic 50% to 79% carotid stenosis by ultrasound with > or =12 months of follow-up were included for multicontrast-weighted carotid MRIs were included. Over a mean follow-up period of 38.2 months, arteries with thinned or ruptured fibrous caps, intraplaque hemorrhage, larger maximum %lipid-rich/necrotic cores, and larger maximum wall thickness were associated with the occurrence of subsequent cerebrovascular events. [23]

MRI imaging techniques have permitted serial monitoring of atherosclerotic disease evolution and the identification of intraplaque risk factors for accelerated progresión. [22]

At last, based upon our research, carotid barochemoreceptor involvement in old patients who died from stroke and suffering obstructive carotid atheromatosis will be discussed. [24]

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2. Pathology

Carotid atherosclerosis is commonly associated with symptoms of cerebral ischemia. However little attention has been directed to intraplaque factors that precipitate the onset of symptoms. [25] On the other hand, the treatment of coronary and carotid atherosclerosis, requires an understanding of the pathogenesis of plaque fissure. [26] Advances in molecular biology, coronary diagnostic techniques and cardiac treatments have suggested new factors leading to plaque fissure. [26-28] It was suggested that the risk of plaque fissure depends on plaque composition rather than plaque size, because only plaques rich in soft extracellular lipids are prone to rupture. [27] Also, it was demonstrated that ruptured plaque caps have much larger transverse gradients of connective tissue constituents than non-ruptured plaque caps, and that the development of these transverse gradients may be critical in determining the propensity of a plaque to rupture. [28] It was also shown that the site of rupture of thrombosed coronary atherosclerotic plaques is marked by an inflammatory infiltration where the macrophages are the dominant cells. [29]

However, the exact mechanisms causing plaque rupture are yet not complete known. [29] In this connection, papers dealing with rupture of carotid plaque surface are few in spite of the growing importance of the subject. [18,19,30] We analyzed in pioneer papers[18,19,30] the cellular and vascular components of surgically excised carotid endarterectomies. Thus, the cell populations involved in the inflammatory activity in atherosclerotic lesions were further characterized with cell specific monoclonal antibodies in order to obtain information about their role in the pathogenesis of plaque rupture and intraplaque hemorrhage.[30] In brief, 76 surgical specimens of 74 patients who were submitted to carotid endarterectomy were used for these studies. There were 55 males and 19 females. Age ranged from 40 to 83 years (mean 69.4 years).Patients were divided into three clinical subgroups: asymptomatic (carotid lumen obstruction > 70%), symptomatic (stable) and symptomatic (unstable). The usual unifying pathologic feature in the plaques was the presence of large lipid cores with a fibrous cap overlying the lipid core and a band of fibrous tissue of varying thickness separating the plaque from the atrophic media (Figure 1). This collagen rim was in general extensively vascularized. Exceptionally the plaque was composed of fibrocellular tissue without a clear lipid core. In most cases, widespread chronic inflammatory infiltrates were observed either in the cap or in the lipid core (Figure 2). In all cases the carotid bifurcation and the first 1.5 cm of the internal carotid were involved.

The result of immunophenotyping of the cellular constituents of the plaques were described in relation to the different layers (from the lumen to the media), namely: Endothelial lining (Anti-CD31 and anti-CD34). The fibrous cap at the site of the rupture/erosion had an eroded surface characterized by loss of the endothelial lining (Figure 3). On the other hand in the remaining surface a continuous, not damaged row of endothelial cells stained with anti-CD31 and anti-CD34 was observed in all cases

Fibrous cap: the collagenous fibrous cap at the site of erosion was attenuated and the phenotypic characterization of the cells showed inflammatory components consisting mainly of macrophages (CD68 positive), approximately 2/3 of the total infiltration (Figure 4). The

remaining 1/3 was composed of T-lymphocytes and rare B-lymphocytes. This pattern was observed in 34/ 41 (83%) of ruptured plaques. A close interaction between macrophages and the abundant capillaries of the lipid cores (Figure 4) and macrophages and T-lymphocytes was commonly observed. Some foamy macrophages showed not only brown staining corresponding to the expression of CD68 but also weak red staining for CD31, thus suggesting that these cells also contain this adhesion molecule. Plaques "at risk" (attenuated fibrous cap, large lipid core and extensive macrophage infiltration) are represented in Figure 1.

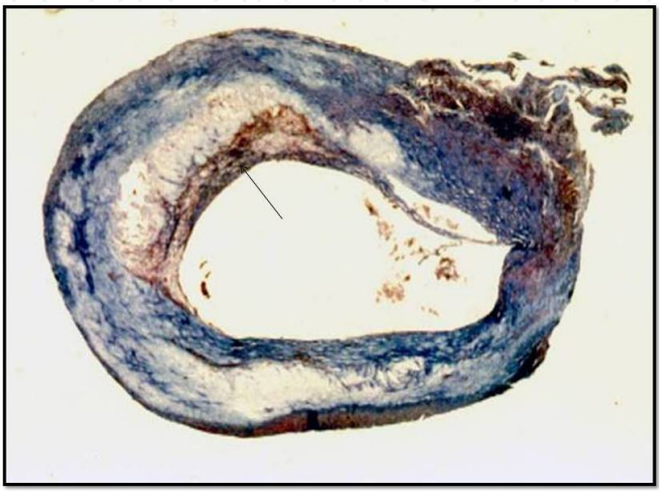


Figure 1. A large lipid core with a thin fibrous cap (arrow) overlying the lipid core is observed.

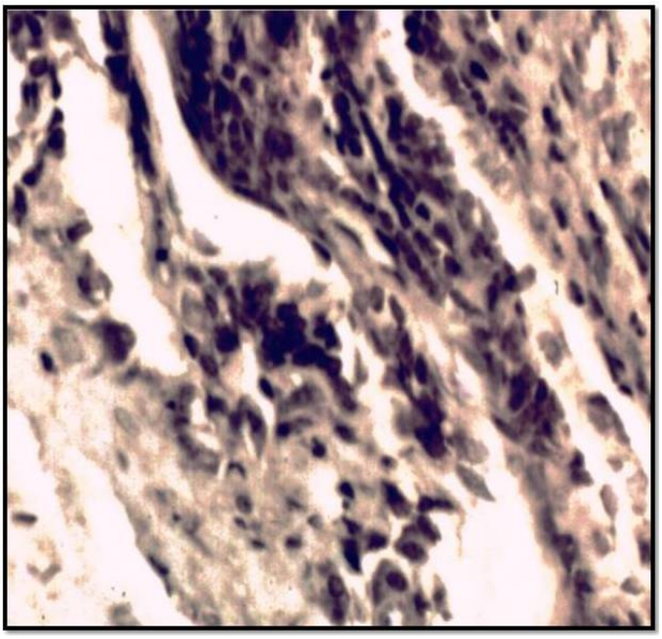


Figure 2. A neoformed thin-walled vessel is shown with lymphocytes migrating to the highly vascularized lipid. Magnification ´250

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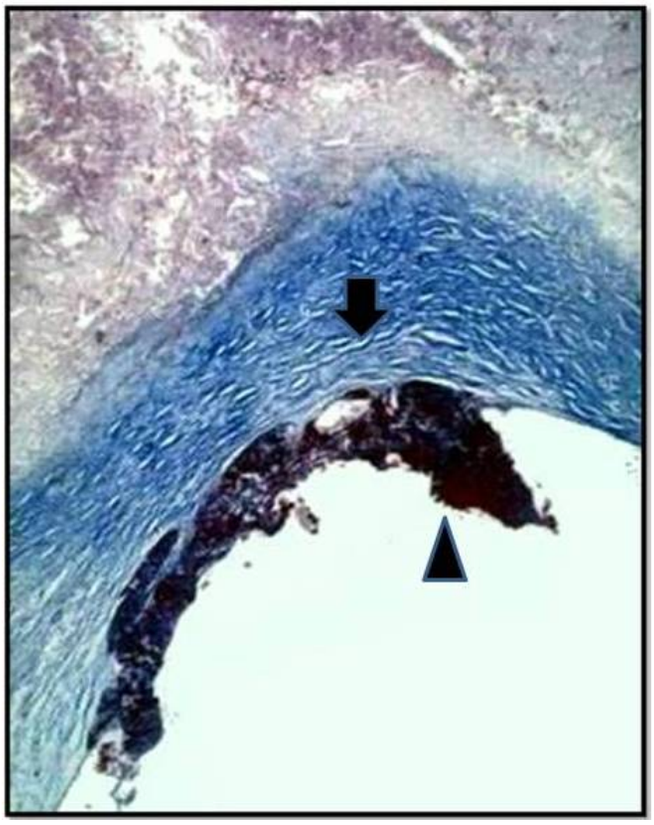


Figure 3. Intraplaque hemorrhage without plaque rupture. Superimposed parietal thrombus. A continuous non ruptured thick cap is shown (arrow). A parietal thrombus is implanted in an eroded surface (arrowhead), and a rich lipid core is heavily embedded by intraplaque hemorrhage(LC).Trichrome-stained collagen, *blue*; hemorrhage, *light red*; thrombus *blue-red* (original magnification _200).

Lipid cores: two different types of lipid cores could be depicted, avascular or mildly vascularized lipid cores and highly vascularized, with neoformed vessels stained with CD34 and CD31(Figure 5 and 6). These vessels varied from proliferated small, thin walled blood vessels to bigger ones, in some cases presenting a hemangioma-like aspect. CD34 stained endothelia of all kind of vessels; conversely, neoformed vessels showed a weak stain with CD31.T-lymphocytes were found to be in contact with neoformed vessels, and in some cases, migrating through the endothelial cells

Media: this tunic was composed of 5 to 12 rows of smooth muscle cells, with their long axes oriented circumferentially, as the edge of the endarterectomy passed through that level. Some thin walled normal capillaries oriented longitudinally to the long axis of the smooth muscle cells were fairly showed by the CD34 and CD31 (Figure 8). Although this tunic did not belong to the plaque itself, it is herein described because of its peculiar vascularization. It is therefore necessary to make a clear distinction regarding the neoformed vessels of the base and periphery of the plaque, and the adjacent capillaries of the media originating from the vasavasorum.

Deeper layers of the plaque: the base and the shoulder of the plaques showed in 28/76 cases neoformed vessels, thin or thick walled, CD34 positive (Figure 7), generally surrounded by mild to extensive mononuclear infiltrates.

Basically atherosclerotic plaques were found to be-long to six different lesions, namely: plaque rupture plus thrombosis (18/76, 23.6%), plaque rupture plus intraplaque hemorrhage plus thrombosis (18/76, 23.6%), intraplaque hemorrhage without plaque rupture (16/76, 21.0%), plaque rupture plus intraplaque hemorrhage (5/76, 6.5%), stable calcified non complicated plaque (14/76, 18.4%) and unstable, soft, non complicated plaque (5/76, 6.5%). The first four lesions were considered as "complicated lesions".



Figure 4. Foamy macrophages show brown staining corresponding to the expression of CD68 and weak red staining for CD31.

- **Plaque rupture plus thrombosis (PR+T).** The fibrous cap overlying the lipid core was highly variable in thickness and cellular constituents. Plaques presented ulcerations with break-down of the surface of the cap. Their-regularity had a punched-out characteristic or was simply a tear with borders; in rare cases plaques contained virtually no fibrous cap. The rupture was covered by a thrombus, and in many cases the thrombus was found directly overlying the lipid core of the lesion, entering a large pool of extracellular lipids. As said the borders of the rupture presented a mononuclear infiltration with a high density of macrophages.

- **Plaque rupture plus intraplaque hemorrhage plus thrombosis (PR+IPH+T).** (Figure 9)The histological findings were similar to the ruptured-thrombosed plaques, but there was also extensive disruption of the plaque by an intraplaque hemorrhage.

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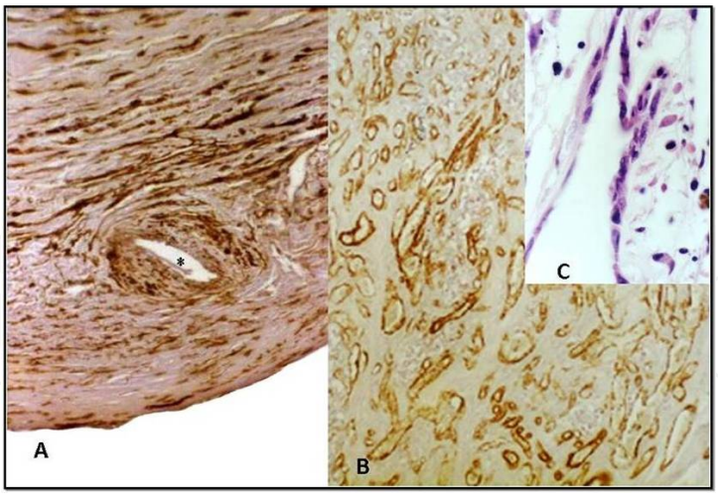


Figure 5. Intense neovascularization of the lipid core. Immunoperoxidase technique for smooth muscle cells (α-actin). In panel A, the asterisk indicates a thick neovascularization vessel. Panel B shows the middle arterial layer. In panel C:,a central neoformed vessel outgrowth in "glove finger" is seen into the lipid core. Endothelial pyknotic cells surrounded by scarse pericytes, macrophages, and lymphocytes in the periphery are shown.

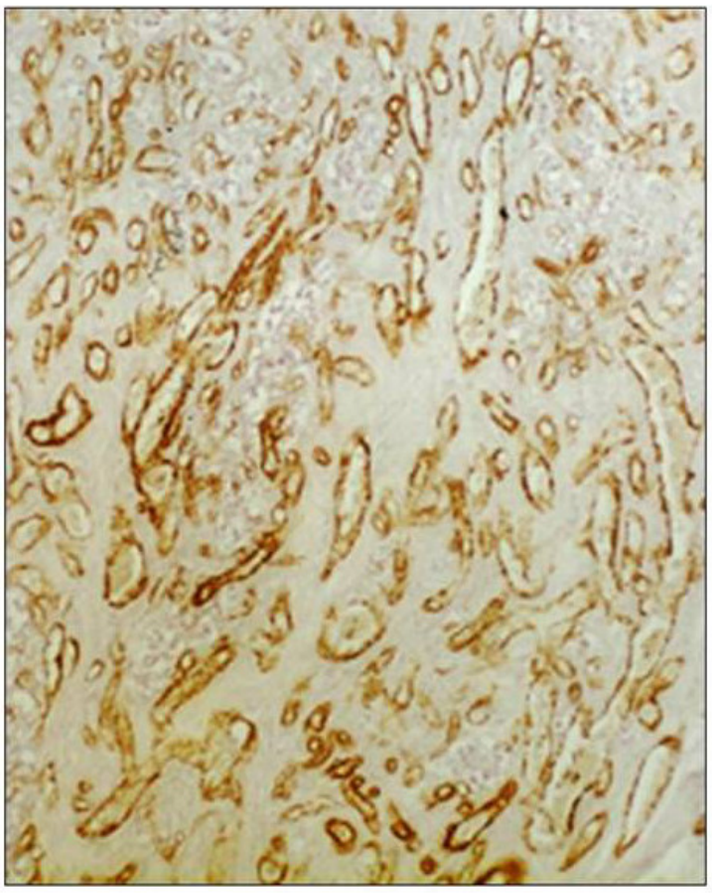


Figure 6. Lipid-rich core is heavily vascularized by great number of thin-walled, neoformed,CD34-positive vessels. Magnification ´250.

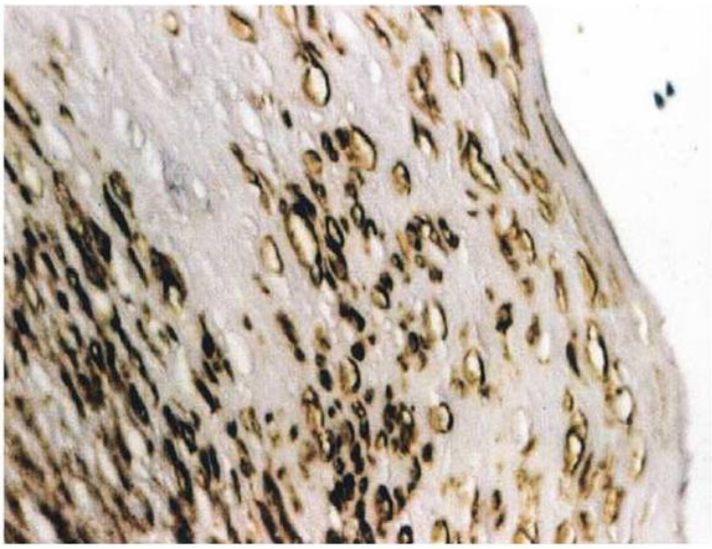


Figure 7. Vascularization of the shoulder of the plaque. Note thin-walled neoformed vessels of different shapes and sizes. Outer zone shows media and an extensive quantity of thin-walled normal capillaries,longitudinally oriented *(brown)*. Antiactin monoclonal antibody(HHF35) was used to demonstrate vascular structures (original magnification _250).

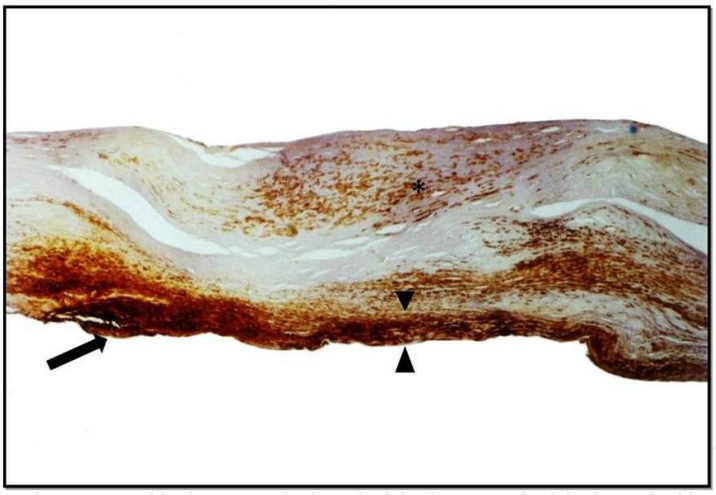


Figure 8. Low magnification view of an entire endarterectomy specimen shows actin-positive vessel walls (HHF35) and hyperplastic smooth muscle cells (asterisc). Media (arrowheads) shows normal arrangement and at this level is composed of only 5 to 10 layers of smooth muscle cells (arrow). Magnification x25.

Intraplaque hemorrhage without plaque rupture (IPH) (Figure 10). None of them had a connection between the hemorrhage and the arterial lumen, in spite of a careful search in serial sections. Conversely the intimal surfaces were clean and none showed evidence or platelet or fibrin deposition. Hemorrhages varied from microscopic, microfocal or slitlike foci of recent hemorrhage, with no evident changes in the overall makeup of the plaque to massive hemorrhage, elevation and disruption of the intima to massive hemorrhage,elevation and disruption of the intima and occlusive stenosis. Only these massive lesions were considered. Of note,

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slitlike hemorrhages distant to the main lesion were found in 12 cases, in 5 of them without the presence of a massive intraplaque hemorrhage.



Figure 9. Plaque rupture (arrow) plus intraplaque hemorrhage and parietal thrombosis. An entire specimen from a carotid endarterectomy frontally cut is shown. 1, Common carotid artery; 2,external carotid artery. *Large lipid core with huge intraplaque hemorrhage with thrombotic components, and small parietal thrombus are observed. Fibrous cap is extremely thin (hematoxylin-eosin; original magnification 3).

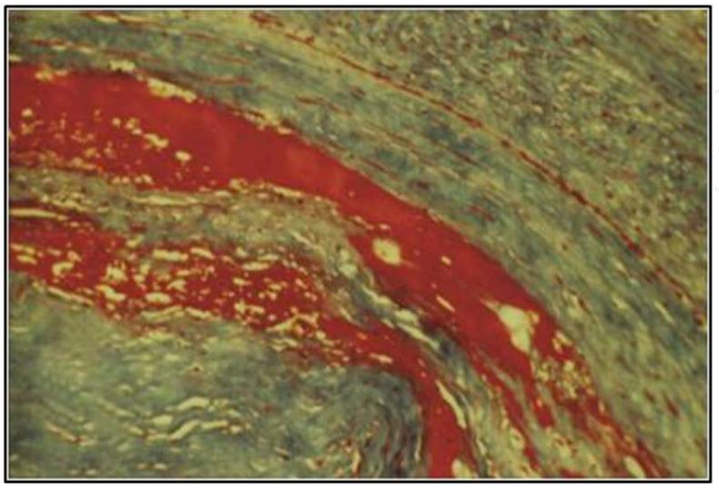


Figure 10. Sample of carotid endarterectomy. Laminar hemorrhage, distal to the main lesion Trichrome-stained collagen, *blue*; hemorrhage, *light red*; Magnification ´250.

Plaque rupture plus intraplaque hemorrhage (PR+IPH) (Figure 11). It was characterized by an extensive hemorrhage within the plaque with separation of its varying components and disruption of the intima.

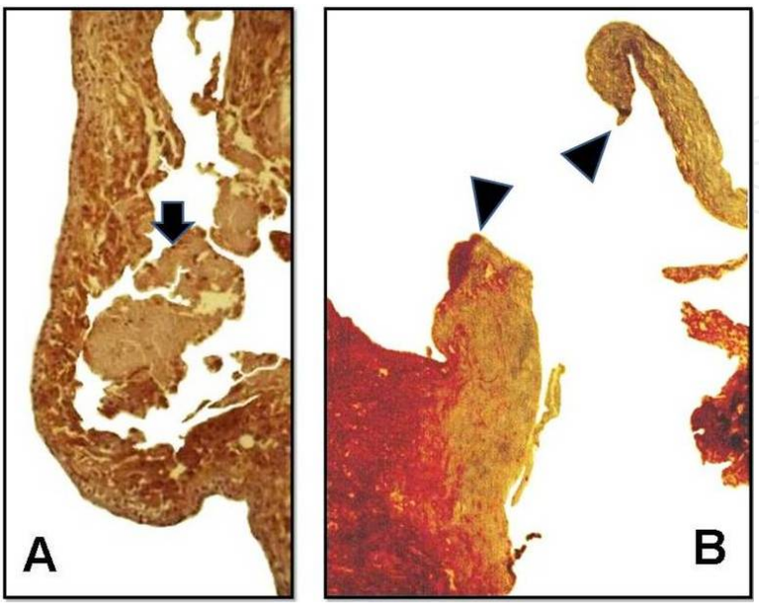


Figure 11. Plaque rupture. A intraplaque hemorrhage (arrow) B-. Breakdown of cap is clearly shown (between arrow-heads)

- **Stable, calcified, non complicated plaque (S+C)** (Figure 12).These plaques contained neither thrombosis nor hemorrhages and consisted of laminated fibrous connective tissue and irregular masses of calcified material. These areas appeared as acellular, roughly circular masses of pale-staining debris.

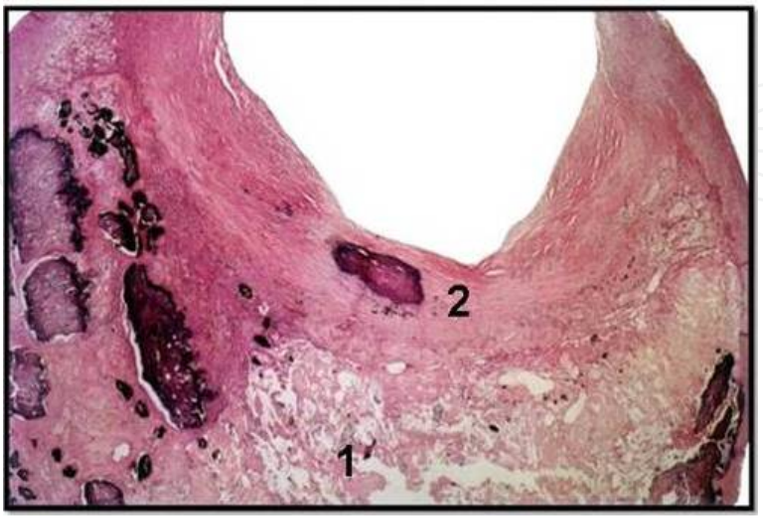


Figure 12. Stable calcified plate. Lipid core (1), thick cover (2), and abundant calcified areas in black

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Unstable, soft, non complicated plaque (U+NC). These plaques consisted of thin fibrous caps covering a lipid-rich core with extensive vascularization. As these are the ingredients of a plaque "at risk", those may be plaques in which rupture hemorrhage and/or thrombosis might have occurred in the future.

Complicated vs stable calcified, non complicated plaques. Complicated plaques presented neoformed vessels in the periphery, shoulder and base of the plaque in 22/57 (38.5%) cases. Conversely only 1/14 (7.1%) of non complicated, stable calcified plaques presented this type of vessels ($p < 0.05$). Of note, the 5 cases of unstable, soft non complicated plaque presented neoformed vessels surrounding the plaque. In 10/57 (17.5%) complicated plaques unequivocal histological signs of old hemorrhages were found surrounding those vessels. Irrespective of presenting no rupture, 11/35 plaques showed a mononuclear in-filtrate in the fibrous cap.

Clinical-pathological correlation. The risk factor variables (age, gender, hypertension, left ventricular hypertrophy, diabetes, weight, smoking and uric acid) could not be correlated with any of the pathological and immunohistochemical findings. Hypertension (70%) and smoking (59%) were the risk factors more frequently found irrespective of the morphological findings.Therefore, carotid endarterectomies provided the material for phenotypic characterization of vascular and cellular components of the plaque. This permitted to known the topography and the distribution of mononuclear infiltrates as well as endothelial cells. Although the cellular composition of advanced atherosclerotic plaques is known to be heterogeneous, [31] it can be summarized as:

Intimal plaque rupture-inflammatory process. We demonstrated for the first time[30] that rupture of carotid plaques is characterized by the presence of a macrophagic infiltration of the caps. The presence of a large number of foamy macrophages in plaque fissuring in human coronary thrombosis had been reported previously [29,32-34] and it was suggested that inflammation through enzymatic degradation of the fibrous cap by macrophages might destabilize the plaque, causing weakening at the immediate site of rupture. In carotid endarterectomies although the fibrous cap overlying the plaque was variable in thickness, the area of rupture was dominated by macrophages as the main cellular component, T-lymphocytes and scarce B-lymphocytes and granulated and/or degranulated mast cells. Complete rupture of the fibrous cap was found to be the cause of thrombosis in 18 cases, intraplaque hemorrhage plus thrombosis in 18 and intraplaque hemorrhage in 5 cases. It means that approximately 50% of carotid endarterectomies have the plaque fissure as the anatomic substratum. Of note, only 23/41 (56%) of these cases have been symptomatic. Our studies in carotid plaques showed direct apposition of T-lymphocytes to macrophages and a close relation of these cells to endothelial cells. This highly suggests a cell-to-cell interaction, which results in an inflammatory process mediated by cellular adhesion molecules (such as CD31), cytokines, growth factors and other substances as described in coronary arteries[29] and aorta. [35] Therefore, the possibility of autocrine, juxtacrine or paracrine secretion was evident. [36]

Intraplaque hemorrhage without plaque rupture-plaque vascularization. Intraplaque hemorrhage without rupture was present in 21% of the endarterectomies. This subset of carotid lesions was not related to cap erosion, but to plaque vascularization. Most lipid cores were highly vascularized with neoformed vessels with macrophages and T-cells in close contact and

some cases disrupting the endothelium The abrupt growing of the lipid cores and/or an overproduction of oxygen free radicals could lead to the breakdown of core vessels and intraplaque hemorrhage. This seems to be the most plausible mechanism. The periphery and shoulder of the plaques had in 30% of the cases neoformed vessels surrounded by extensive mononuclear infiltrates. Theseneoformed vessels showed a weak stain with CD31. Considering that CD31 (PECAM-1) is a molecular adhesion molecule, the lack of expression could be pointing out a functional difference between normal and neoformed vessels. PECAM- 1 is required for transendothelial migration of leucocytes.

The same mechanism postulated for the vessels of the core may operate in neoformed vessels. The presence of histological signs of old hemorrhages and the existence of slitlike hemorrhages at that level strongly suggest that a local origin of bleeding may operate. Lusby et al[25] demonstrated that the resultant angiogenesis associated with hemorrhages might make those lesions prone to mechanical stress and subsequent hemorrhages. Accordingly, our observations and those by other authors suggest that intraplaque hemorrhages may occur at any time in the history of carotid plaque. [37] Hypertension may be a predisposing factor in the rupture of neoformed vessels and the development of the hemorrhage within the plaque.

Our results in 76 endarterectomies suggest that the site of plaque rupture is associated with the presence of a large macrophagic infiltration, [38] as well as T-lymphocytes rare B-lymphocytes and mast cells and lack of smooth muscle cells. These peculiar type of plaque should be considered as a "plaque at risk”[29] in addition to plaques containing large amounts of lipid pools and a thin fibrous cap. [34] Conversely, intraplaque hemorrhages without plaque rupture might be due to the breakdown of neo-formed core vessels and/or neoformed vessels of the base and shoulder of the plaque.

The decision of whether to perform endarterectomy in patients with asymptomatic disease should be made on the basis of data including degree of stenosis and activity of the carotid lesion, as well as issues of medical and surgical morbidity. [39]

The relationship between anatomy of carotid plaques and the presence or not of symptoms. For this purpose we carried out an investigation[19] in order to analyze in a large sample the relation between the anatomy of carotid plaques and the presence of symptoms in 281 endarterectomy specimens. To avoid an excessive number of plaque subtypes that might blur the relationship with symptoms, [31] only complicated and non-complicated plaques and ruptured and nonruptured plaques were used for statistical analysis. Patients (mean age, 68 +/-8 y.o.,range,40-84 y.o.) were 213 men (mean age, 68 y.o.s; range, 45-83 y.o.) and 68 women (mean age,68.7 y.o.; range, 40-84 y.o.).[19] In all cases the bifurcation and the first 10 to 15 mm of the internal carotid artery were involved. In 196 plaques, large lipid cores with a fibrous cap and a band of fibrous tissue separating the plaque from the remainder of the media were observed. The cap was frequently vascularized. In most cases, extensive inflammatory infiltrates consisting of macrophages, smaller numbers of T lymphocytes, a few B lymphocytes, and mast cells were observed. In the remaining cases, the plaque was composed of fibrocellular tissue only.[19]

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For statistical purposes, plaques were divided into two subsets: **complicated** (types PR+T, PR +IPH+T, PR+IPH, ulcerated calcified plaques and IPH) vs. **non-complicated**, and **ruptured** (types 1 through 4) vs **non-ruptured** (types IPH,S+C and U+NC).

Complicated plaques (205 of 281) exhibited mononuclear infiltrates in the periphery, shoulders,and bases in 137 of 205 (67%) plaques, compared with only 22 of 76 (29%) noncomplicated plaques ($p< 0.001$). Complicated plaques demonstrated neoformed vessels in the periphery, shoulders, and bases in 146 of 205 (71%) plaques, compared with only 38 of 76 (50%) noncomplicated plaques ($p<0.001$). Twelve of 18 unstable, soft, non complicated plaques exhibited neoformed vessels surrounding the plaques. The remaining 6 plaques had huge lipid cores without evident neoformed vessels, suggesting very recent development. In 34 of 205(17%) complicated plaques, old hemorrhages were found surrounding neoformedvessels. Ruptured versus non-ruptured plaques. Infiltrates were noted in the caps and shoulders in 108 of 130 (83%) ruptured plaques and 22 of 151 (15%) unruptured plaques ($p< 0.0001$).External carotid arteries arteries exhibited typical histopathologic findings of advanced atheromatosis in 51 of 281 cases(18%).Only 2 of 51 affected cases demonstrated complicated plaques.This resulted in a significant difference when compared with the internal carotid artery ruptures (1of40 vs 85 of 165 $p< 0.001$).Risk factors could not be associated with any pathologic findings. Hypertension (74%), smoking (61%), hyperlipidemia (61%), and diabetes mellitus (24%) were the risk factors most frequently noted. No correlation could be established between plaque type and symptoms (Table I). Of note, although 99 of 205 (48%) complicated plaques were found in patients with symptomatic disease, a high percentage (106 of 205, 52%) were also found in patients with asymptomatic disease. The same was observed for ruptured plaques; 67 of 130 (52%) were found in patients with symptomatic disease, compared with 63 of 130 (48%) in patients with asymptomatic disease. No relation could be found between symptomatic versus asymptomatic disease with regard to old hemorrhage (18 [12%] vs 26 [19%]), distal IPH(19 [13%] vs 13 [10%]), laminar hemorrhage (14 [9%] vs 22 [16%]), and parietal thrombosis (14 [9%] vs18 [13%]).

Differences in flow velocity profiles and wall shear stress might explain the lower atherosclerotic involvement and rare complications of the external carotid artery as compared with the internal carotid artery (205 of 281 vs 2 of 281; $P<0.0001$). Areas of carotid plaque rupture were characterized by macrophagic infiltration at the rupture. This finding suggests that inflammation, through enzymatic degradation of the fibrous cap by macrophages, might destabilize the plaque, causing weakening at the site of rupture.[25,30,40] Complete rupture of the cap (46% of cases) was the cause of thrombosis in 7%, IPH plus thrombosis in 18%, and IPH in 19%. Therefore plaque rupture was the cause of thrombosis in only 25% of cases. Many factors can modulate the development of thrombus. Long-term preoperative administration of aspirin and use of heparin during surgery may explain the relatively low frequency of thrombosis observed in ruptured plaques. Other possibilities are that fibrin or platelet deposition was missed at previous embolization orduring microscopic examination because of sampling. However, inasmuch as excisionwas *in bloc*, without "touching" the lesion, thrombus displacement seems unlikely. IPH without rupture represented 27% of endarterectomy specimens in the present study. This subset of lesions was not related to rupture of the cap, but to plaque

neovascularization. Lipid cores were highly vascularized with heterogeneous neoformed vessels and with macrophages and T cells in close contact with the endothelial wall. An increase in the amount of lipid in the core, mechanicalstresses,[25] and overproduction of oxygen free radicals by macrophages could lead to breakdown of core neoform vessels and IPH production.[27] The same mechanisms might also act in neoform vessels in the periphery of the plaques. Old hemorrhages in 17% of complicated plaques and presence of distant slitlike hemorrhages strongly suggest that the bleeding may be of local origin.[30,41] Hemorrhages were attributed to mechanical stress of turbulent flow and to wall vibration secondary to stiffness of the carotid wall,[30] and have also been associated with an increase in matrix metalloproteinase 1 expression in the macrophages of the fibrous cap, suggesting a role for inflammatory mediators in vessel disruption.[31] Therefore, IPH may occur at any time in the course of a carotid plaque.[18,30,37,38]

Complicated and noncomplicated plaques versus symptomatic and asymptomatic disease. Plaque rupture was present in 46% of endarterectomy specimens. However, only 67 of 130 (52%) of these were found in patients with symptomatic disease. On the other hand, a high proportion of patients with asymptomatic disease (48%) demonstrated complicated plaques.Coronary plaque ruptures have been identified in patients who died of noncardiac causes.[18] Accordingly, occurrence of carotid plaque rupture or hemorrhage without symptomatic manifestation seems likely.The frequency of plaque hemorrhage and plaque disruption varied greatly among the various series from both symptomatic and asymptomatic specimens In a review of several studies,[25,37,42-46] Fisher et al observed that the pooled frequency of plaque hemorrhage and rupture demonstrated a significantly increased frequency in the symptomatic group. However,pooling data from multiple sources when methods of analysis are different (histologicvs macroscopic) is hazardous. [47] Therefore studies in which only macroscopic assessment was performed[25,37,48-53] must be discarded. Some authors stress that IPH indicates only the severity of atherosclerosis;[50,51,54-57] others suggest IPH has a direct role in pathogenesis of transient ischemic attack or stroke. [25,35,44,46,57] When most studies are considered, the incidence of IPH in symptomatic and asymptomatic disease spreads considerably In the symptomatic group, incidence varied from 17% to 97%, compared with 2% to 91% in the asymptomatic group. In the European Carotid Plaque Study, [58] a high incidence of IPH was observed in symptomatic (94%) and asymptomatic (71%) groups A higher incidence of IPH was reported in patients without symptoms.[55,59,60] Lennihan et al[54] scored the occurrence of IPH only in patients with symptoms, and found ipsilateral symptoms in 57% of patients with IPH and 65% of patients without IPH, indicating little difference between the two groups. IPH seems to be more common in plaques causing high-grade stenosis.[47,54,55] Carr et al[52] found patients with symptomatic plaques to have more frequent plaque rupture, fibrous cap thinning, and cap foam cell infiltration, compared with patients with asymptomatic plaques. IPH was also seen in all specimens from symptomatic specimens and in 68% of asymptomatic specimens. However, this study included too few patients to be significant. Despite a close relationship between IPH and symptoms,[37,61-63] and carotid plaque rupture, thrombosis, and symptoms, [25,60,61] it has also been claimed that patients with

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symptomatic plaques typically have large necrotic cores within the carotid arteries.[31] Some studies indicate that the association of complicated plaque and symptomatic disease does not exist.[55,62-64] It is conceivable that patients presumed to have no symptoms might have had embolic episodes and that emboli became impacted in silent cerebral areas or occurred during sleep.[25,37,44,57] Also, symptoms may not be recalled by patients, who are often elderly or frail. Of note, in a high-risk subgroup of patients with asymptomatic carotid stenosis the annual stroke rate was more than 4%.[33] Inzitari et al[10] confirmed that cardioembolic and small vessel stroke can occur, in addition to large vessel athero-thrombotic stroke, in patients with asymptomatic carotid stenosis. Finally, NASCET[3] demonstrated that most carotid strokes occur without warning symptoms, and only 5% to 15% of patients have a transient ischemic attack as an impending symptom of stroke. Nevertheless nowadays carotid endarterectomy or stenting should not be performed in asymptomatic patients except those in which some clinical conditions are present, as recommended by the American Heart Association/American Stroke Association. [65]

Patients with asymptomatic carotid artery stenosis should be screened for other treatable risk factors for stroke with institution of appropriate lifestyle changes and medical therapy (Class I; Level of Evidence C).

1. Selection of asymptomatic patients for carotid revascularization should be guided by an assessment of comorbid conditions and life expectancy, as well as other individual factors, and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences (Class I; Level of Evidence C).

2. The use of aspirin in conjunction with carotid endarterectomy (CEA) is recommended unless contraindicated because aspirin was used in all of the cited trials of CEA as an antiplatelet drug (Class I; Level of Evidence C).

3. Prophylactic CEA performed with <3% morbidity and mortality can be useful in highly selected patients with an asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound) (Class IIa; Level of Evidence A). It should be noted that the benefit of surgery may now be lower than anticipated based on randomized trial results, and the cited 3% threshold for complication rates may be high because of interim advances in medical therapy.

4. Prophylactic carotid artery stenting (CAS) might be considered in highly selected patients with an asymptomatic carotid stenosis (≥60% on angiography, ≥70% on validated Doppler ultrasonography, or ≥80% on computed tomographic angiography or MRA if the stenosis on ultrasonography was 50% to 69%). The advantage of revascularization over current medical therapy alone is not well established (Class IIb; Level of Evidence B).

5. The usefulness of CAS as an alternative to CEA in asymptomatic patients at high risk for the surgical procedure is uncertain (Class IIb; Level of Evidence C).

6. Population screening for asymptomatic carotid artery stenosis is not recommended (Class III; Level of Evidence B).

Other points to consider is the necessity of interventionally treating an asymptomatic carotid artery disease are: age 80 years or less, life expectancy higher tan 5 years, hemispheric hypoperfusion, significant intracerebral vascular disease,unstable carotid plaque, rapid progression of the stenoses, presence of silent cerebral infarcts, neck radiotherapy and the necessity of a coronary by pass surgery. [66-74]

As it can be seen, up to date criterium for percentage stenoses in this group of patients are higher than in the ACAS study (60%). [75]

Finally and taking into consideration the mechanisms of atherosclerosis: cells component behavior, IPH, biology and gene expression, it can be seen in the literature a new tendency of treatment in animal models. However, attention should therefore focus on the processes of plaque breakdown andt hrombus formation in humans, whereas the use of animal models should probably be reserved for studying the function of particular genes and for investigating isolated features of plaques,such as the relationshipbetween cap thickness and plaque stability. [76] In this connection, Peter et al [77] described a ApoE(-/-) mice mouse model reflecting human atherosclerotic plaque instability in which atorvastatinwas used aimed at preventing plaque rupture. They concluded that distinctly expressed genes andmicroRNAscan be linked to plaque instability.On the other hand, Forte et al described the role of polyamines in reducing carotid arteriotomy-induced (re)stenosis s in vitro and in a rat model suggesting a novel therapeutic approach for this pathophysiological process. [78]

3. Plaque morphology

The atherosclerotic process in the carotid arteries begins with a thickening of the intima-media complex and, according to factors of disease progression can reach arterial occlusion, throughout intermediate stages of mild, moderate and severe stenosis. Moreover, depending on several factors, the structure of the plaque can show different evolutionary behaviors, from simple stable plaque, fibrotic, and non stenotic, to that hemorrhagic, ulcerated, with rupture that produces severe stenosis and strokes. Carotid risk factors are identical to those mentioned for coronary disease.[79,80]

3.1. Correlation between plaque morphology and cerebral symptoms

The incidence of cerebrovascular events depends primarily on the degree of carotid stenosis but plaque structure is also relevant, as well as the speed of progression of plaque, and consequent carotid disease stenosis and also the presence of systemic thrombogenic factors. [81-83]

Several studies have described a good correlation between intraplaque hemorrhage (IPH) with ulceration and cerebrovascular symptoms.[25,53] According to Bluth the plaque structure is even more important than the degree of stenosis, in predicting neurologic events. [84]

Bearing in mind than more than 40 % of the patients with transient ischemic attacks later may suffer a stroke some authors believe that these stroke occur because plaques with IPH are

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unstable.[25,28,53] Embolization of fibrin and platelets and/or atherosclerotic material from the plaque itself will continue.

As was mentioned, Geroulakos et al[81] classified ultrasonographic carotid plaques in 5 different types of stenosis, and correlated plaque type with symptomatology (not with pathology), showing the predominance of echolucent plaques in symptomatic patients with stenosis > 70 percent (see below) From the histologic point of view it was found that 50 % of the IPH had connections with the lumen while 20 % had not.[30] Lusby et al[25] showed that "haemorrhage in carotid atheromatous plaques plays a unique and major role in the development of cerebrovascular disease". IPH was not only identified in most symptomatic patients but also a close relationship was established between the onset of symptoms and the presence of plaque haemorrhage. Seeger et al[81-85] reported that the composition of plaques from symptomatic patients is significantly different from those asymptomatic. The former contains more total lipid and cholesterol, and less collagen and calcium.

Johnson et al [86] classified asymptomatic plaques according to ultrasonographic characteristics into calcified, dense and soft. At the end of a 3 year follow-up a large proportion of asymptomatic patients with soft plaques had become symptomatic, while a small proportion of those with calcified plaques have developed symptoms. Hennerici et al [87] reported that patients with fibrous carotid plaques had a tendency to remain stable while plaque progression was common in those with soft and complex calcified plaques. Spontaneous regression of minor carotid atheroma occurred in soft plaques corresponding to a reduction in plaque volume while fibrous and calcified plaques did not regress. [87]

Despite that currently the presence of symptoms and percentage of luminal narrowing remain the most useful predictors of transitory ischemic cerebral attacks or stroke risk, [3,75,88,89] there is a body of evidence that plaque morphology is crucial in the development of its natural history.

Regarding the relationship of IPH with a higher prevalence of symptoms or hemorrhagic stroke, the results are contradictory. [23-64] However, current guidelines recommend reporting the plaque structure in question and that in occasions define therapeutic behaviors. [82-83]

There are several reasons that make knowledge of plaques structure very important. It is well known that fibrous plaques, are predominantly collagen in content, showing a highly echogenic quality and being generally homogeneous in texture. When lipid content of the plaque increased, the plaque turns more echolucent. [84] Complex plaques protrude more frequently into the lumen presenting high incidence of surface irregularities and ulcers. [60] Several authors found that the incidence of IPH, histologically assessed, in symptomatic carotid stenosis is higher than 90 %. [25,44,53,99] Imparato et al, prospectively studied 376 carotid artery plaques concluding that IPH was strongly associated with the presence of cerebrovascular symptoms and it was the main characteristic of the carotid plaque that correlated statistically with the presence of symptoms. [44] O´Donnel theorized that IPH is the most common morphologic characteristic in symptomatic patients. [60]

3.2. B-mode ultrasound and pathology correlation

In the 80´s, several authors attempted to describe plaque morphology and the presence of ulceration by ultrasonographic imaging. However, results were not convincing [90,91]. Other authors mentioned only relevant the percentage of carotid stenosis [92,93].

The accuracy of the carotid ultrasonography procedure in assessing the percentage of luminal diameter narrowing is well established [94,95].Percentage of stenosis has been the main point of interest for noninvasive carotid testing due to its correlation with stroke risk.[96,97]

Developed technics in ultrasound (US) permit a more detailed analysis and accurate information about the plaque morphology. This technique is useful to evaluate the natural history and the stroke risk associated to the lesions.

High-resolution B-mode ultrasonography (B-mode) seems advantageous over arteriography for characterizing atherosclerotic plaque. [53] The method can identify those lesions that place the patient at risk for transient ischemic attacks.

It was suggested that echolucent plaques have increased lipid and cholesterol levels, making them unstable and prone to rupture and hemorrhage. On the other hand, the echogenic plaques which contain significantly more fibrin and collagen are more stable and therefore less likely to cause complications. [81,85] There is a paper correlating these two ultrasonic types of plaques with whole frontal and/or transverse histological sections, correlating the B mode ultrasonographic diagnosis of at carotid arteries with their respective pathological examinations assessing US accuracy. [98]

According to Lehay, [99] Bluth, [84] Goes [100] and the recommendations from the Committee on Standards in Non - invasive Vascular Testing, [101] carotid plaques were classified as homogeneous or heterogeneous. But these two groups arose from categorizing the plaques into 4 types according to the scale of l to 4 based on the Geroulakos' classification [81]. In this classification, Type 1 corresponded to uniformly sonolucent; type 2, predominantly sonolucent; type 3 predominantly echogenic and type 4 uniformly echogenic. In this way types l and 2 corresponded to heterogeneous plaques and types 3 and 4 to homogeneous plaques. (Figures 13 and 14)

The analysis of the complex plaque structure regards defining histological types [98]:

- Thrombus, described “a brightly eosinophilic mass of compacted fibrin and degenerating erythrocytes sometimes accompanied by evidence of organization".
- Ruptured plaque was defined as "disruption of the fibrous cap of a lesion that provoked exposure of the thrombogenic lipid core region to the flowing blood and was classified histologically as an irregular plaque surface with breaks in of loss of the fibrous cap often associated with surface thrombus directly overlying the lipid~rich necrotic core of the lesion"[26]
- Inflammation was described as chronic inflammatory infiltrates (lymphocytes, histiocytes, macrophages and mast cells) within the plaque itself. Hemorrhage was identified by a

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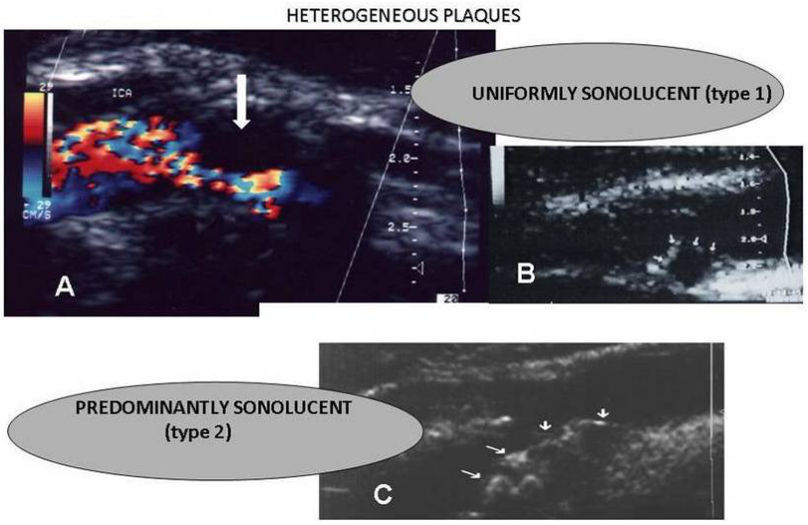


Figure 13. Panels A and B correspond to type 1 plaques-. The arrows indicate fully anechoic stenotic plaques which may correspond to fatty tissue and / or blood which indicate the instability of the same. Panel C Carotid plaque type 2 showing dense echoes (white color) alternating with most hypoechoic or anechoic areas(in black) which indicate plaque instability

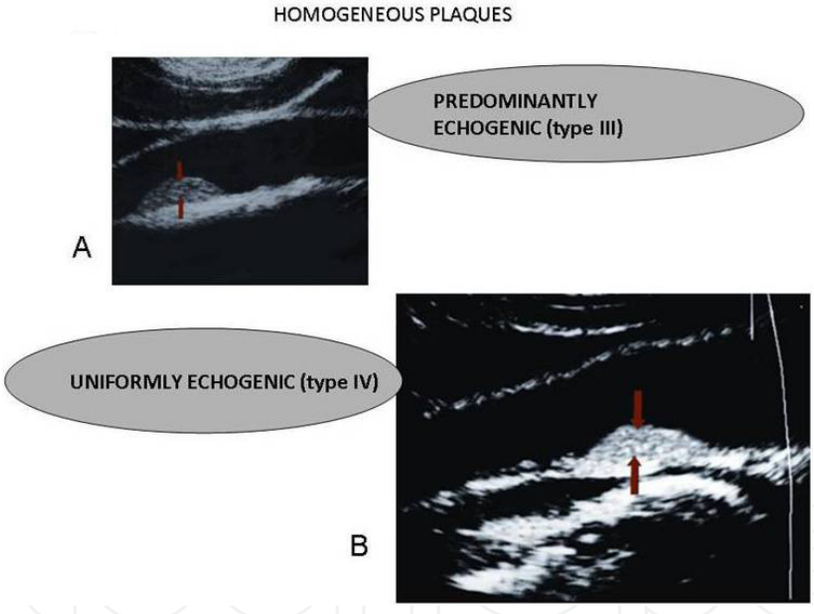


Figure 14. Panel A: it can be seen between arrows a carotid plaque containing predominantly echogenic areas (type 3)that generally correspond to fibrous tissue which gives it stability Panel B.This carotid plaque (type 4) is practically composed by echogenic areas (between arrows).

macroscopic hematoma within the arterial wall with or without extension through the luminal surface.

- Hemorrhage is identified by disruption of red blood cells and macrophage engulfment of hemosiderin, to distinguish it from surgical related hemorrhage consisting in preserved erythrocytes.

Plaque morphology analyzed by US, identifying those unstable or complicated plaques found a very good correlation unless calcium deposits exist. [98]

Ultrasonographically, calcium deposits are characterized by a highly echoreflective area with acoustical shadowing masking the real plaque structure below, resulting in a worse correlation between US and pathology.

Carotid plaques having calcium deposits correspond to a third classification (stable, unstable and calcium), as their evolution can be unpredictable. The presence of "acoustic shadows" that mask the true tissue structure is characteristic of this type of plaque on ultrasonography, making morphological interpretation difficult. [81] (Figure 15)

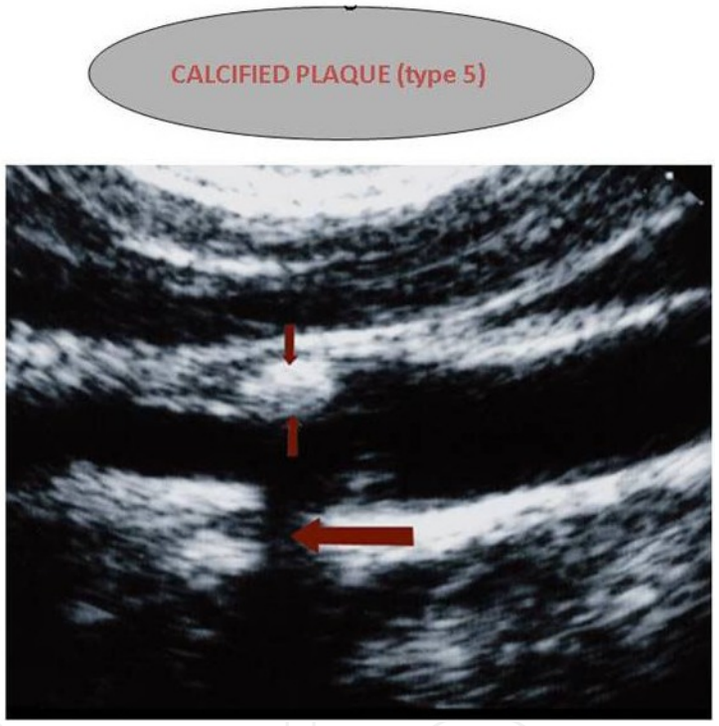


Figure 15. A type 5 calcified carotid plaque significantly reduces the lumen in the carotid bulb (between small arrows) The typically acoustic shadowing is clearly seen (big arrow)

In this sense, we published the results of an investigation showing ultrasonic vs pathologic correlation of carotid atheromatous plaques. This manuscript involved two ultrasonographers and one pathologist. [98] This work implied seventy-four carotid ultrasonographic studies randomly selected from a registry of 250 carotid endarterectomy specimens. (Thirteen of them had poor quality images and were excluded). The remaining 61 studies, belonging to 59 patients (2 bilateral endarterectomies) had been sent from five different laboratories and were analyzed blindly and independently by two different observers. There were 17 females and 42 males. Age ranged from 52 to 83 years (mean 68 years). A very good interobserver correlation was observed and, in turn, with histopathological findings. However, calcium plaques produced less agreement.

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In our research regarding interobserver agreement, there were 2 non-coincidences vs. 59 coincidences (efficacy 98%), K = 0.956, demonstrating very good agreement.

Regarding the strictly classification in heterogeneous, homogeneous and calcified plaques, there were 59 coincidences, (96.7%) and 2 non-coincidences (3.3%), accuracy 98 %, K = 0.95 (very good agreement).

Coincidences not always were total. If we consider the fourth group in which operators agreed in plaques being heterogeneous but with difficulties in distinguishing IPH, calcium and lipids as non-coincidences, then the accuracy falls to 88.5 %.

When we considered agreement between observers and pathologist and taking into consideration the overall results from both observers, there was an agreement of 84% with the pathologist. When calcified plaques were not considered it is expected with 95% of confidence that US will agree with pathology in 70-93% of the cases (CI0,95).

When calcified plaques were considered, the percentage of coincidence fell to 67% (CI 0,95 54-79%). In others words calcified plaques clearly blurred the diagnosis of plaque structure. Operator l had an agreement of 67% with 18% of calcified plaques. Operator 2 had an agreement of 79% with 8% of calcified plaques.

Regarding the coincidence of IPH between B - mode and pathology, operator 1 had an agreement of 50% (11/22) while operator 2 agreed in 65 % of the cases (11 / l7). The pathologist diagnosed IPH in 33 cases, therefore both observers, together were able to detect IPH in only l / 3 of the cases.

This investigation has correlated the ultrasound aspect of carotid atheromatous plaques with pathology demonstrating the highest incidence of intraplaque hemorrhage (IPH) in those complex, irregular and heterogeneous producing stenosis 98. (Figure 16)

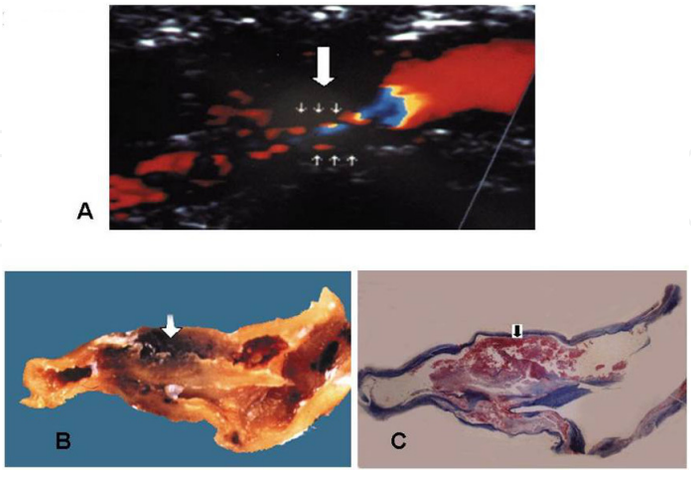


Figure 16. A.Two dimensional and color ultrasound image displays a very tight stenosis (between arrows) caused by an anechoic plaque (large arrow) B. The corresponding gross morphology shows an irregular stenotic plaque composed by a brownish tissue (arrow). C. Microscopically this plaque belongs to an intraplaque hemorrhage (arrow). Mallory Trichrome

Correlation with histology shows that lipid rich regions are the least echogenic on US and calcified areas are the most. [81,98] Dense collagen is also very echogenic not associated with acoustic shadowing. For example O´Donnel [60] emphasized that plaque haemorrhage could be differentiated from lipid-laden plaque because the former was more irregular, echolucent, frequently associated with irregular borders, and randomly distributed through the plaque producing a non-homogeneous texture. The surface of the plaque with hemorrhage is usually irregular and ulcerated. Surface ulceration is unusual in lipid plaques. By contrast, plaque hemorrhage produces an echolucent area within the plaque, in which its degree may be correlated with the age of hemorrhage. [60]

The anechoic or highly echolucent qualities of fresh hemorrhage are comparable with those of the lumen, being irregular and randomly distributed through the plaque (heterogeneous shape).

On the other hand, Bluth et al [84] found that the incidence of IPH in theheterogeneous type was 81 % vs. 3 % in the homogeneous plaques. Thus, the sensitivity and specificity of US to detect this lesion was 94 % and 88 % respectively.

Ultrasonography fails in detecting plaque ulceration even using color-flow Doppler assisted duplex, as was recently demonstrated by Sitzer et al. [102]

Hartmann et al [103] reported poor results between US and pathology concluding that visual assessment of B-mode images is not reliable. Lehay et al [99] found that plaques that caused a narrowing greater than 50% in the carotid lumen were more likely to be heterogeneous, suggesting that plaque appearance is a more relevant finding on preoperative duplex scanning than the percentage of carotid narrowing.

Taking all these concepts into consideration, decreased echogenicity would correspond either to lipid deposits or to hemorrhage within a plaque being both of them characteristic of instability. Lipid deposits appear more uniform and are less randomly distributed throughout the plaque.

Julian et al [104] divided plaques into two categories: "simple" composed of fibrous material and that do not generally cause stenosis greater than 50 %, and "complex" consisting of an atherosclerotic material, calcified deposits, surface fibrin, platelet material and hemorrhagic areas.

The European Carotid Plaque Study Group [105] correlated B-mode imaging studies with histology in 270 patients undergoing carotid endarterectomy. They concluded that US appearance of carotid plaque is related to histological composition being the echogenicity inversely related to the relative amount of soft tissue.

Backscattered radiofrequency derived signals devices have been applied for better characterization of the different components of plaque structure[106-108].But this technique is more expensive and not always available in most laboratories so we consider that conventional good quality B-mode images allow a reliable differentiation between the three types of plaques.

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3.3. Magnetic resonance imaging – Patholgy correlation

Although carotid ulltrasound is the method of choice to study the structure of carotid plaques MRI also plays a significant role. Singh et at, [109] in an interesting paper describing structural MRI findings in 98 asymptomatic carotid arteries with moderate stenosis (50-70%) and subsequent one year evolution to symptomatic status: 36 (36.7%) had IPH on NMR, with 6 cerebrovascular events, ie 16%, (2 stroke and 4 AIT) related to carotid IPH showed, compared to the absence of events in the carotid without IPH. Their statistical analyzes confirmed that the detection of IPH on NMR was associated with an increased risk of cerebrovascular events. In another relevant work involving MRI, Cheung et al [110] investigated the presence of IPH in the carotid arteries of 217 patients who had symptomatic stenosis less than 50%. IPH was detected in 13% related to the hemisphere ipsilateral symptoms and 7% contralateral.

In summary, we believe necessary to describe and report the B-mode characteristic of carotid plaques together with the percentage of luminal stenosis. Ultrasonic plaque description correlates with histogy. The adoption of plaque characterization despite of the degree of carotid stenosis would allow recognition of a high-risk subset of patients that may benefit from carotid intervention.

4. Carotid artery dolichoarteriopathies

Atherosclerosis is the most frequent cause of extracranial carotidartery disease. [111] However, although atheromatous pathology of the carotid bulb and bifurcation is a major causes of stroke, other causes of carotid disease may also cause vessel occlusion, such as fibrodysplasia, trauma (with subsequent dissection of carotid arteries), aortic arch pathology as in Takayasu disease, and aortic dissection. [112]

Among nonatheromatous alterations of the carotid arteries, interest has long been placed on specific anatomical abnormalities called dolichoarteriopathies.

Carotid dolichoarteriopathies can be classified into three different types [113](Figure 17).Type 1: tortuosity – a nonrectilinear stretch of an artery with an angulation >90; type 2: loop – a 360 angulation of an artery on its transverse axis (''coil'' configuration) (Figure 18); type 3: kinking – the inflection of 2 or more segments of an artery with an internal angle of 90° or less. (Figures 19 and 20).

Dolichoarteriopathies of carotid arteries are frequent, ranging between 10% and 45%. [114] For type 3, a prevalence of 5% to 25% has been described.[115,116]

Published studies have reached disparate conclusions with regard to the origin or cause of carotid dolichoarteriopathies, as well as their hemodynamic and prognostic significance. [114-119] Mukherjee and Inahara [119] proposed that carotid kinking would induce turbulent flow, thus favoring intimal ulceration, platelet deposition, and distal thrombus embolism. Other investigators similarly believe that a causal connection exists between cerebral flow alteration and severe carotid dolichoarteriopathies, to the point of proposing surgical correction of kinking and coiling to prevent stroke. [14,120,121]

Conversely,other authors consider carotid dolichoarteriopathies as a mere anatomical variety, devoid of clinical consequences. [122]

Establishing the clinical impact of dolichoarteriopathies is further complicated by the fact that the mechanisms responsible for their formation are still debated.

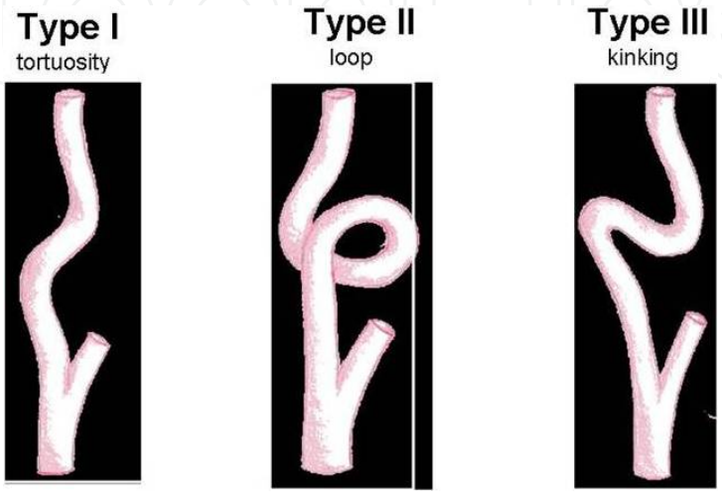


Figure 17. The different types of dolichoarteriopathies, according to the definition of Weibel and Fields.

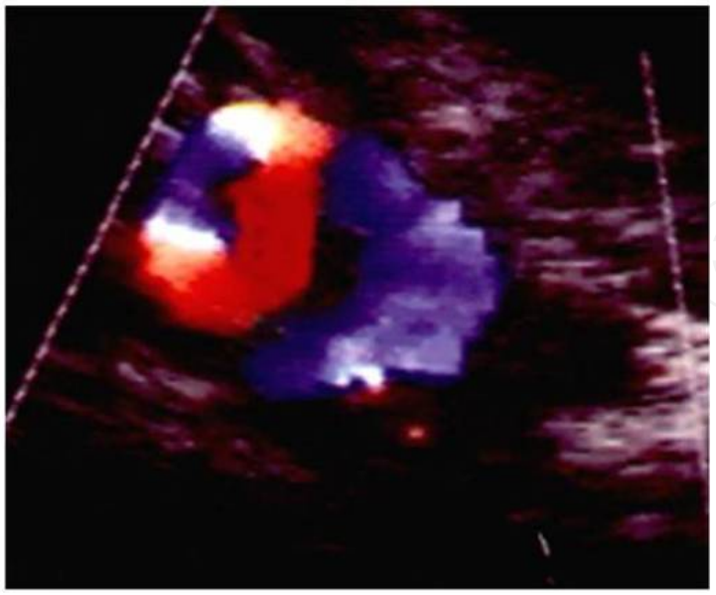


Figure 18. Color flow Doppler imaging shows circular-shaped internal carotid artery

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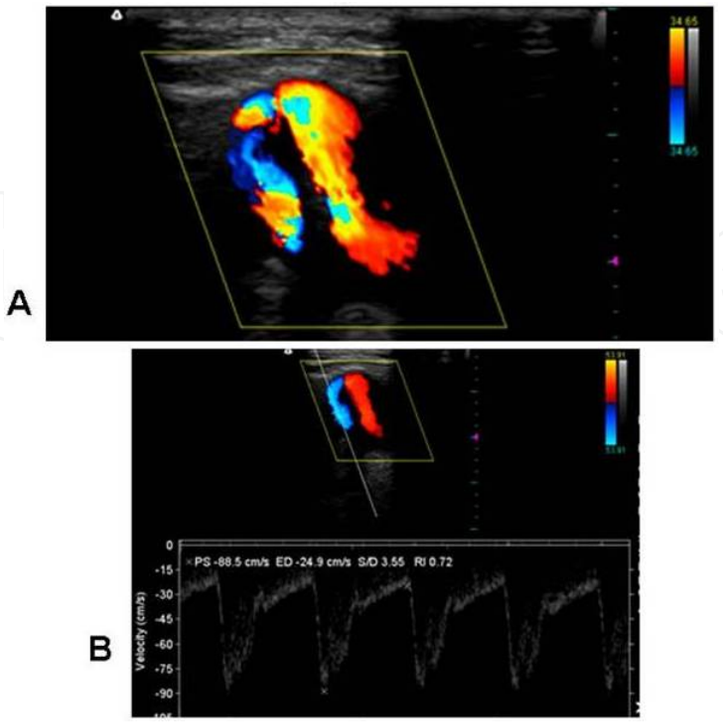


Figure 19. A: Color flow Doppler imaging discloses an internal carotid artery kinking.B: Color and pulsed-wave Doppler showed turbulences at the site of the kinking. However, both maximum systolic velocity and end-diastolic velocity of internal carotid arteries were substantially unaffected by kinking

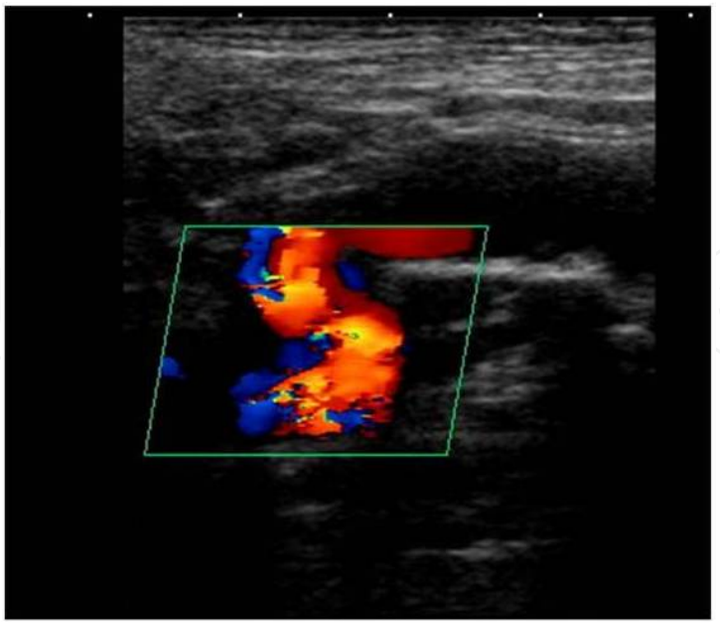


Figure 20. A double angled internal carotid artery showing a S shaped configuration (image corresponding to color Doppler ultrasound)

4.1. Origin of carotid dolichoarteriopathies — Congenital or acquired?

One theory maintains that they are pathological alterations caused by arterial aging and/or changes induced by atherosclerotic remodeling, which would cause the vessel to bend, [114,123-126] while other reports do not support an association between dolichoarteriopathies and cardiovascular risk status. [122,127,128] Alternatively, it has therefore been postulated that they have an embryological origin. Indeed, Kelly [129] observed that carotid arteries may be kinked or show loops at some point during intrauterine development, when the descent toward the mediastinum occurs enabling the union of the third aortic arch with the dorsal aorta.

Obviously, as these 2 etiological theories are so different from each other, they may also entail different implications both clinically and prognostically. Part of the uncertainty derives from the fact that previous observations had been made in small studies or in selected populations. [122-128] Therefore, it would be important to establish which theory has more solid basis.

Prevalence varies according to different diagnostic methodology and patients' inclusion criteria, but in aggregate they concur to indicate that this is a rather frequent finding. In contrast, lack of consensus exists over the clinical and prognostic significance of these alterations or even about their etiology. Much of the controversy revolves around a ''nature- or-nurture'' type of issue, that is, whether carotid dolichoarteriopathies develop late in life as a manifestation of vessel remodeling, particularly in individuals at risk of atherosclerosis, or rather they originate from alterations of embryological development.

With regard to the possibility that dolichoarteriopathies may be the result of a degenerative process, over the years several hypotheses have been put forward trying to explain how they may develop. Some of these seem quite unlikely, such as the possibility that carotid kinking could be due to kyphosis or lordosis of the spine, which might deviate the carotid axis, [130] or that inflammation of the tissues around the carotid arteries would cause them to retract. [131] Other investigators have proposed that arterial hypertension would produce alterations in the wall over time, which would favor its weakening withsubsequent kinking of the artery, [121-123] while other authors hypothesized a relationship between aging and arterial anatomical abnormalities. [114,126]

Data gathered in modern times also do not help in establishing firm conclusions. Two rather large reports by Ghilardi et al [125] and Del Corso et al [132] described a great prevalence of hypertension and atherosclerosis in patients with carotid dolichoarteriopathies; however, both studies lack a group of normal participants, and deal with a population of patients selected for vascular pathology, and in whom predominance of such cardiovascular risk factors is expected. Pancera et al [127] have reported an association between carotid artery kinking and age and with hypertension as well. However, in that study, prevalence of carotid abnormalities was actually identical across the age groups from 60 to>80 years, which represented 87% of their cohort: younger patients, in whom prevalence was apparently lower, were instead too few to make a solid comparison. This same reasoning applies to the effect of hypertension reported in that study, which was actually based on about a dozen patients. [127]

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The possibility that carotid dolichoarteriopathies may have an embryological origin had also been suggested in the past. Again, however, those reports were not conclusive. Sometimes, this was because of the small numbers of cases studied. In this respect, Weibel and Fields [113] described at angiography 14 cases of anatomical abnormalities in patients aged between1 and 20 years, while Sarkari et al [133] reported 8 children (aged 9 months to 16 years) with symptomatic carotid kinkings and coilings. In a substantially largerstudy, there may have been a selection bias [134] in that case, 282 angiographies of neck vessels were obtainedin patients aged between 6 months and 82 years. The authors found that prevalence ofcarotid abnormalities in adults was 24% and even greater (43%) in children. Although that finding may seemingly support the view that in fact there is no association with aging and that dolichoarteriopathies have an embryological origin, the significance of such a high frequence in children might have been restricted to the peculiar population studied, as it is quite conceivable that children who were subjected to an invasive procedure such as angiography underwent it because of a high clinical suspicion of carotid abnormalities.

Togay-Isikay et al,through noninvasive Doppler ultrasonography assessment, observed carotid dolichoarteriopathies in 24.6% of a consecutive patient series, with no apparent relation between carotid alterations and cardiovascular risk factors. [122] In 1924,Cairney [135] had already reported autoptic findings in fetuses from the fifth month in whom morphological carotid arteries abnormalitieswere observed. In this respect, it is important to notice that the vascular wall in fetus develops from mesenchymal cells islets; in any artery, the tunica muscularis develops first in the main trunk and later in its branches. The proximal portion of the internal carotid artery originates from the third aortic arch while the more distal parts originate from the left dorsal aorta. [130] Harrison and Dávalos [130] suggested that development of carotid arteries and of skeletal system might be asynchronous, the different velocity explaining the tortuous path.Ochsner et al [136] proposed that fibromuscular dysplasia occurring during fetal life, located in a sector of the carotid artery, would be responsible for subsequent weakening and kinking of the wall at that level. Contrary to this specific hypothesis, however, is the fact that presence of fibromuscular dysplasia in areas with dolichoarteriopathies is very rare.[137-139]

Regarding the issue of congenital or adquired condition of dolichoarteriopathies, our group conducted an observational study involving 885 participants of either sex, aged between newborn(4 hour 30 minutes) to 90 years old. [16]

Patients were divided into 2 groups (G): G1 (control, healthy participants) n = 245. It consisted of infants, children, and adolescents up to 15 years of age (mean 6 + 3 years) from a town of 43 000 inhabitants just outside of Buenos Aires; these children participated in a voluntary screening health program, approved by their parents, under the patronage of the local municipality that was performed in the hospital and different schools. Group 2 (G2; n = 640) consisted of patients from 16 to 90 years of age (mean 57+8 years) in whom diagnostic color Doppler ultrasonography investigation of neck vessels had been requested for clinical suspicion of atherosclerotic disease. Patients were assessed with regard to presence of cardiovascular risk factors (hypertension, dyslipidemia, smoking). Presence of atheromatous plaques in the regions affected by dolichoarteriopathies was also evaluated.

Coiling prevalence was similar in healthy participants (G1 4%; n ¼ 10) and in patients (G2 3%; n = 19; NS;). At the same time, kinking prevalence in G1 was 27% (n = 67), and it was 22% (n = 143) in G2, which did not show any statistically significant association either Atheromatous plaques intrakinking were only observed in 3 G2 patients (0.47%). In this group, 56.2% of patients presented carotid atherosclerotic disease. Within G2 patients, prevalence of cardiovascular risk factors evaluated individually was similar when patients were divided according to presence or absence of kinking and/or coiling.

We observed that the dolichoarteriopathies, namely, kinking and coiling of carotid arteries, had similar frequency across all ages, from newborn infants to elderly individuals. Furthermore, their prevalence was unrelated to the presence of cardiovascular risk factors or of frank atherosclerotic pathology of carotid artery. Collectively, these findings suggest that carotid dolichoarteriopathies are a result of alterations in embryological development rather than of vascular remodeling secondary to aging and/or atherosclerosis. [16]

5. Hemodinamical behavior of dolichoarteriopathies: Ischemic or not?

As was previously mentioned, there a wide span of clinical consequences have been atributed to the presence of carotid dolichoarteriopathies, ranging from asymptomatic carotid anatomical variety to carotid induced cerebral ischemia. [122] As referred, Mukherjee et al [119] proposed that carotid kinking would generate distal thrombus embolism, by means of the turbulent flow, intimal ulceration and platelet deposition. Surgical correction of kinking and coiling carotid arteries has been proposed to prevent stroke. [14,121]

The prevalence of cerebrovascular symptoms in patients with carotid dolichoarteriopathies varies between 15 and 23%. [140-141] But, there is not uniform criterion about the role of carotid dolichoarteriopathies in the development of neurological symptoms. If dolichoarteriopathies were certainly responsible for these events, cerebral ischemia could be demonstrated by functional hemodynamic tests.

In 1997, Oliviero et al. [128] demonstrated, in 36 patients suffering from hypertension and with kinks, that the percentage of neurological events was similar to the other 36 patients with hypertension but without kinks. The same author published new results of the follow-up of these patients, confirming the former conclusions as in the group of hypertensive patients with kinkings there were 10 neurological events registered, whereas 14 occurred in the control group (hypertensive patients without kinkings). [142]

Several previous papers [62,120,121,143-157] considered that carotid dolichoarteriopathies can produce neurological symptoms and proposed surgery and furthermore, they describe different surgical techniques.

A recent report of 7 kinkings of internal carotid arteries, defined five asymptomatic, one syptomatic for odynophagia and another symptomatic for pharyngeal bulge considering that no typical clinical symptoms were shown in the malformation of cervical segment of internal carotid artery. Pharyngeal bulge with pulsation could be encountered.

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Grego et al. [156] assured that natural history of carotid dolichoarteriopathies is practically unknown but in some cases surgery would be justified, such as: a) transient ischemic attack (hemispheric symptoms); b) asymptomatic patients with a kinking angle less than 30° together with contralateral carotid occlusion; c) patients with non-hemispheric symptoms after evaluating that there were no other possible neurological or non-neurological causes through positive results of the following studies: 1) Doppler ultrasonography of neck vessels with increase in circulatory velocity; 2) computerized cerebral tomography and MRI angiography of ischemic lesions in the ipsilateral hemisphere and 3) Inversion of the circulatory flow in the anterior cerebral artery and its reduction in the middle cerebral artery, in both cases in relation to the rotation and flexo-extension maneuvers of the head.

Recent papers regarding surgical intervention on carotid arteries kinking, totalizing roughly 150 patients, flaw to show convincing evidence on the benefits of intervention.[158-160]

Up to now, there are no guidelines nor is there consensus (with a level of recommendation) for surgical treatment of dolichoarteriopathies.

Taking into account the pitfalls in measuring stenotic percentage in bended arteries, it is our point of view that manuscripts reporting big number of operated patients with carotid dolichoareriopathies failed in the diagnostic ultrasonographic criterions of stenotic kinkings and coils, furthermore, there is no mention about which method for angiographic measures were used. Also, most of their patients had cardiovascular risk factor which could have been the responsible of the neurological symptoms remaining doubts about their true relation with carotid abnormalities. [157,161]

Our group conducted an investigation study regarding the clinical implications in the genesis of neurological complications related to kinking and looping (coiling) of the carotid arteries. [162] Sixty patients with non-atheromatous carotid kinkings were subjected to head rotation tests, and were studied by carotid artery B-mode, color Doppler ultrasonography, and scanning the ophthalmic artery in order to assess the hemodynamic behavior of carotid dolichoarteriopathies. Results suggested that carotid dolichoarteriopathies are not the cause of neurological events or symptoms taking into account that no events were recorded during the study, and registering significant reduction in the velocities in the ophthalmic artery in only 3 of the 60 cases studied, in performing the head rotation tests.in the patient cohort. 23 % (n=14) were asymptomatic as only 6 patients were referred for stroke or transient ischemic attack. Consecuently we concluded that carotid dysembryoplasias, would not cause neurological events nor symptoms.

Computerized tomography angiography (CTA) and magnetic resonance angiography (MRA) showed excellent ability to depict the malformation of cervical segment of internal carotid artery and its relationship with surrounding structures, which could protect carotid artery from unintended damage. [163]

It may be concluded that dolichoartheriopathies recognize a congenital origin other than an acquired condition, based on controlled studies regarding juvenile control cases. Additionally, in the current state of knowledge, it unlikely appears that these dolichoartheriorpathies induce relevant symptomatic cerebral ischemia

6. Carotid sinus baroreceptor

The significance of the ability of the carotid sinus baroreceptor to sense and regulate blood pressure has been known since Hering's publications in 1927. [164]. Later, in1930, Heymans unequivocally demonstrated the chemoreceptor activity of the carotid (or glomus) bodies. [165] However, there have been few human necropsies and therefore, evidence relies on case patients with damage to the carotid sinus and glomus following surgery, radiotherapy and carotid endarterectomy. [166,167] Therefore, little information is available on the morphology of barochemoreceptor structures in disease. [168]

The baroreflex is very important for the maintenance of arterial pressure, particularly during orthostatic stress. Chemoreflexes play an important role in maintaining blood gas homeostasis. [169] Thus, barochemoreflex failure is a disabling and potentially life-threatening condition. Data on the long-term effect of human bilateral carotid sinus denervation on arterial blood pressure are limited and controversial. [166,170-173]

In patients submitted to bilateral tumoral carotid glomus resection it was found a long-term effect on the level, variability and rapid reflex control of arterial pressure included increased daytime and nighttime blood pressure variability, unopposed sympathetic activation in response to physical and mental stress, and the elimination of orthostatic hypotension and normocapnic hypoxic drive as a result of peripheral chemoreflex failure. [174] Barochemoreceptors are compromised in diseases such as diabetic autonomic neuropathy, Guillain-Barré syndrome, arterial hypertension and heart failure. [175] Fatal complications in most stroke patients likely result from baroreceptor malfunction. [175]

The available experimental and clinical evidence suggests that a pattern of chronic intermittent hypoxia, with short episodes of hypoxia followed by normoxia, selectively enhances the chemosensory and ventilatory responses of the carotid body to hypoxia, suggesting this sensor has an essential role in the enhanced ventilatory and cardiovascular responses observed in animals and obstructive sleep apnea patients. [176]

In a previous study we found a strong involvement of the chemoreceptor structures and corresponding supplying arterioles in a selected group of elderly patients who had died from cerebral vascular disorders with critical carotid artery lesions. [177] Despite the accepted dogma that the amount of connective tissue separating the glomic lobules increases with age, [166] the significant fibrotic involvement and the unquestionable reduction in the vascularity, could not merely be explained by the aging process. However, a possible limitation to the interpretation of those results was the superposition of arterial hypertension, atherosclerosis and aging in the patients.

Due to these facts, and to characterize the potential damage of the carotid glomus related to hemodynamic stress alone, we performed experiments using spontaneously hypertensive rats (SHRs), an animal model with arterial hypertension, in which other factors such as dyslipidemia, high blood sugar or aging were absent. In SHRs, we found a significant increase in extracellular matrix expansion in the carotid glomus and autonomic nerves, along with a decreased number of neurons in autonomic ganglia compared with normotensive controls.

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All these findings were highly correlated with high blood pressure and an increase in plasminogen activator inhibitor 1 (PAI-1) and transforming growth factor beta-1 (TGF-β-1) deposits in the carotid glomus and autonomic ganglia. Additionally, SHRs presented a higher wall to lumen arteriole ratio in small periglomic vessels, a higher number of S100 protein-positive cells (sustentacular or type 2 cells) and a decreased number of type 1 cells in the carotid glomus. Interestingly, extracellular matrix expansion was highly correlated with the blood pressure level. Because of this, these structures must be considered as target organs in the model of systemic hypertension. [178]

Our group carried out an investigation in which the objective was to morphometrically characterize the alterations of the carotid barochemoreceptor structures and their supplying arteries in patients who died from stroke with complicated versus noncomplicated internal carotid atheromatosis. [179] For this purpose, samples consisting of bilateral or unilateral carotid segments were obtained at autopsy from 23 elderly patients who died from ischemic neurological disorders. Transient ischemic attacks preceding their strokes, with extensive cerebral damage precipitated their deaths.

Plaques were pathologically characterized) into seven categories (see page 3). [18]

Patients were also divided arbitrarily by age. Group 1 was older than 80 years, Group 2 was 65 to 80 years and Group 3 was younger than 65 years of age. The carotid bifurcation and the first 10 mm to 15 mm of the internal carotid artery were involved in all cases by atherosclerotic lesions. Large lipid cores with a fibrous cap and a band of fibrous tissue of variable thickness separating the plaque from the extensively damaged media were observed in all plaques. In one-third of cases, extensive calcified deposits were also found. The collagen border was frequently vascularized. In most cases, extensive chronic inflammatory infiltrates were observed, consisting of macrophages and minor numbers of lymphocytes as well as extensive neoangiogenesis and calcified deposits. Complicated plaques presented with mononuclear infiltrates in the periphery, shoulders and bases in two-thirds of the cases. In contrast, only one-third of noncomplicated plaques had inflammatory infiltrates ($P<0.0001$).

The carotid glomus was located in the carotid fork, measuring approximately 3 mm X 1.5 mm, and formed by lobules compactly arranged, separated by connective tissue [177,180-182] (Figure 21). The functional units consisted of numerous small groups of cells arranged in clusters. They were grouped to form lobules organized as compact nests that were embedded in a fibrous stroma through which numerous nerve fibrils and small blood vessels were observed (Figure 22). Parenchymal cells consisted of two types: the 'chief cells' (epithelioid or type 1 cells), which were large cells with a round nucleus and a large amount of cytoplasm containing vesicles and granules stained by the Grimelius silver reaction; and elongated cells, known as 'sustentacular cells' or type 2 cells. Chief cells were arranged in the centre and sustentacular cells at the periphery. [177] Complex arrangements of afferent nerves and postganglionic sympathetic nerves, as well as autonomic ganglion cells, were found surrounding the lobules. [181] The carotid glomus showed moderate atrophy and fibrosis to severe atrophy with extensive fibrosis (cirrhotic appearance) (Figure 23).

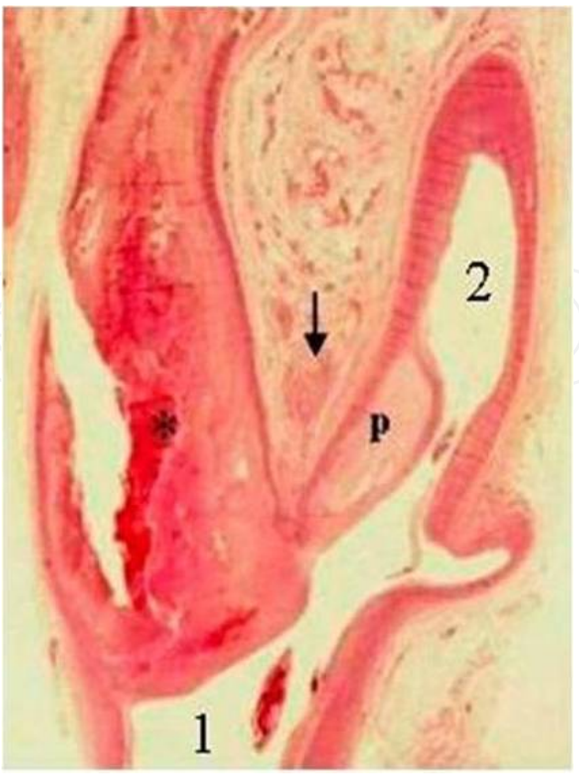


Figure 21. Whole specimen of a frontally cut carotid segment. The arrow points to the glomus located in the interstitial tissue between the internal and external carotid arteries and its corresponding nerves. Multiple nonstenotic fibrolipidic and fibrotic plaques are observed along the carotid axis.Also an intraplaque hemorrhage is shown (asterisk)Hematoxylin and eosin stain; ×20 objective lens. 1 Common carotid artery;2 External carotid artery showing an atheroma inside (P)

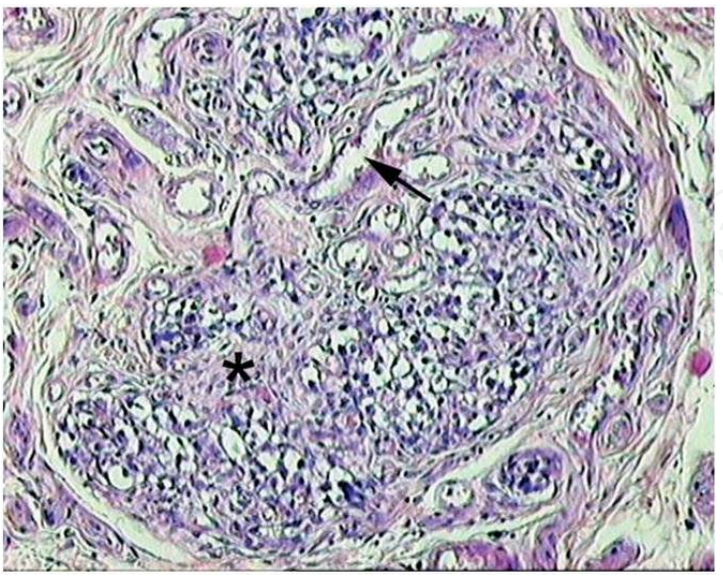


Figure 22. Carotid glomus showing almost normal structure and vascularization.Veins are dilated (arrow) and there is a mild increase in interstitial fibrosis (asterisk). Hematoxylin and eosin stain; ×100 objective lens

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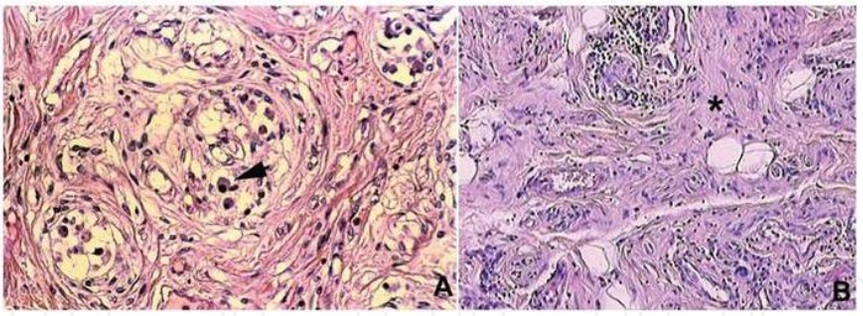


Figure 23. Carotid glomus. A Marked decrease in cells and moderate fibrosis. Typical rounded chief cells are shown in the centre of the section (arrowhead).Hematoxylin and eosin stain; ×400 objective lens. B Severe atrophy and, in some areas, absence of acinar structures with replacement by dense connective tissue with a so-called 'cirrhotic' appearance (asterisk). Hematoxylin and eosin stain; ×100 objective lens

There was a loss of the characteristic chief cells (more than 50%) and loss of their argyrophilic Grimelius-staining granules, suggesting a decrease in their catecholamine content. Fibrosis and glomic cell loss was assessed as 2.6±0.5. A focal reduction of glomus vascularization (more than 50%) was also observed in the areas of atrophy and fibrosis when capillaries were stained with anti-CD34, which was assessed as 2.76±0.6 (Figure 24) In a few cases, it was possible to observe autonomic ganglia showing moderate fibrosis, mild-to-moderate neuronal damage and lipofuscin deposits (Figure 25). Interestingly, the arterioles to the glomus showed severe fibrointimal proliferation and disruption of the internal elastic lamina, marked thickening of the media and luminal narrowing. Luminal thrombi were also observed, as well as focal areas of medial homogenization (Figure 26). At the outer media of the carotid sinus, corresponding to the deeper layers of the plaques, it was possible to identify damaged nerve endings that reacted specifically with S100 protein. No differences were found among groups for glomus area, number of type 1 cells, number of type 2 cells or the wall to lumen arteriole ratio. Also, no statistical differences could be demonstrated when complicated (intraplaque hemorrhage and/or rupture and/or thrombosis) and noncomplicated plaques were compared or when comparing age groups 1, 2 and 3. No correlation between morphometric data and age was found. Patients with stenosis of the extracranial carotid arteries constitute a multimorbid population that frequently shows several vascular risk factors, including hypertension and diabetes. Our study [179] demonstrated that, in patients who died from cerebral vascular disorders with critical carotid artery lesions, a strong involvement of the chemoreceptor structures and their supplying arterioles was found.

Accordingly, at the outer media of the carotid sinus, corresponding to the deeper fibrocalcified layers of the plaques and in periglomic areas, damaged nerve endings were observed as well as fibrotic autonomic ganglia. Therefore, a strong involvement of the baro-(carotid sinus) and chemoreceptor (carotid body or glomus) structures and their corresponding nerves and arterioles was observed in the group of elderly patients. These lesions were independent of patient age, as well as the presence of a complicated carotid plaque. Despite the observation that the connective tissue separating the glomic lobules increases with age, [166] the marked fibrotic involvement and the clear decrease in its rich vascularity, shown by the CD34 immunophenotyping, cannot be explained only in terms of aging. Several studies have found the

grade of fibrosis to be dependent on age, [183] while others have demonstrated considerable differences, not only within comparable age groups but, in a few cases, between the right and left sides. [184]

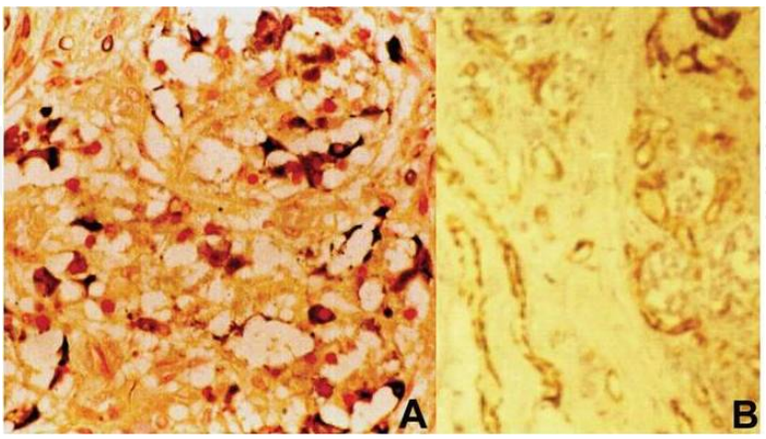


Figure 24. A :Acinar structure belonging to a carotid glomus showing a moderate-to-severe decrease in the number of chief cells, and loss of argyrophilic intracellular granules (shown in black). Grimelius stain; ×200 objective lens. B: Carotid glomus. A focal absence and global decrease of vascularization is shown in the areas of acinar atrophy and fibrosis. anti-CD34 stain; ×100 objective lens

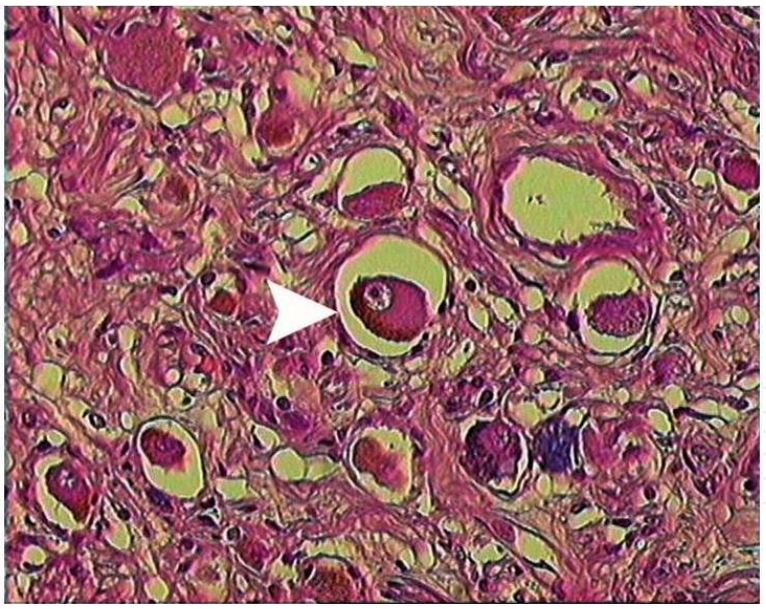


Figure 25. Autonomic ganglia showing moderate fibrosis and mild-to moderate neuronal damage with intracytoplasmic lipofuscin deposits (arrowhead).Hematoxylin and eosin stain; ×200 objective lens

On the other hand, examination of surgical specimens removed from patients older than 60 years of age showed that the organ almost had a 'cirrhotic' appearance. [181] This suggests an arteriolar involvement leading to fibrosis by a chronic hypoxic mechanism. Most of the autonomic parameters, including heart rate variability and baroreflex sensitivity, decline with

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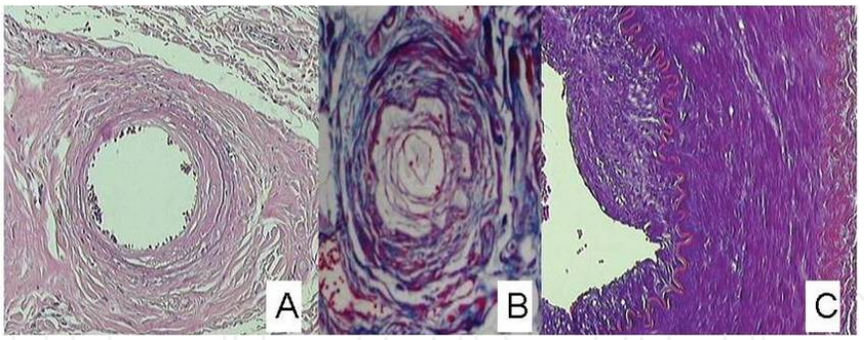


Figure 26. A::Glomic arteriole showing marked intimal fibrosis with moderate thickening of the media and focal areas of medial homogenization, and severe adventitial fibrosis. Hematoxylin and eosin stain; ×100 objective lens. B: Glomic arteriole with marked fibrointimal proliferation and thickening of the wall with luminal narrowing. Azan stain; ×100 objective lens. C: Small artery supplying the glomus. Marked fibrointimal fibrosis with reduction of the lumen and medial fibrosis. Azan stain; ×100 objective lens

age. [185] However, in the rat, aging of the cardiovascular system may not be associated with the attenuation of the baroreflex function. [184] Accordingly, the carotid baroreceptor reflex is well maintained in both young and old dogs, suggesting a lack of morphological involvement. [186] Nevertheless, the attenuation of the baroreflex is far less pronounced in patients in whom the possible effects of disease counteract the age effects. [187]

Therefore, it is possible that the age-related baroreflex attenuation observed in humans may not be due to aging *per se* but may instead reflect atherosclerotic and/or hypertensive processes. [188-189] There are few data concerning the dependency of the various kinds of chemoreflex sensitivity on age in healthy human subjects. A study [185] however, showed no significant correlation between chemoreflex sensitivity and age in patients with multiple organ dysfunction syndrome. The authors hypothesized that this lack of correlation can be interpreted as a confirmation that the effect of the disease prevails over aging in pathological conditions.

Early studies [187-189] speculated that a high systemic arterial pressure may deactivate the baroreceptor function by damaging the nerve endings in the arterial wall. An alternative explanation was issued by Heath and Smith, [190] who suggested that an increased stiffness of the arterial wall would splint the baroreceptor endings, reducing their sensitivity to changes in arterial pressure instead. These authors pointed out that, to some extent, atherosclerosis must depend on the orientation of the receptors in the arterial wall. If they are pulled circumferentially, an increased rigidity of the arterial wall should lead to a decreased baroreceptor response. In contrast, if the structure is compressed outwards from within, an increased rigidity of the vessel wall may not have such an effect. [191]

Baroreflex is aroused by changes in blood pressure that are collected by autonomic nerve 'sensors' that are distributed in the arterial tree and convey the stimuli elicited by mean pressure, rate of change in pressure (dP/dt), pulse pressure and heart rate. These mechanoreceptors, typically gathered in the outer tunica media of the carotid sinus, are found as nerve terminals and, occasionally, with the features of drumstick swellings. The smooth muscle layer is thinner there to allow for an increased vessel compliance favouring an enhanced mechanical stimulation. [192]

Adjustment of the respiration rate in response to changes in levels of oxygen, carbon dioxide and hydrogen ions in body fluids are mediated by a complex interplay between central and peripheral chemoreceptors. The peripheral arterial chemoreceptors, located in the carotid and aortic glomus, are responsible for the immediate ventilatory and arterial pressure increments during acute hypoxia. [165] Type 1 cells in the carotid and aortic glomus release neurotransmitters in response to hypoxia, causing depolarization of nearby afferent nerve endings. [191,192]

Unquestionably, permanent high blood pressure causes a deleterious effect in peripheral nervous structures. However, few studies deal with the findings reported in our papers [18,177,178] regarding the deleterious effect of arterial hypertension on carotid glomus and autonomic ganglia.

As said, our studies in SHRs has demonstrated a strong correlation between arterial hypertension and the development of lesions in the carotid glomus and autonomic ganglia characterized by extracellular matrix expansion, as well as a reduction in the number of ganglia neurons. [178]

Because lowering blood pressure is the first step in controlling the deleterious effects of arterial hypertension, we have evaluated the possible differences between the effects of the beta-blocker atenolol (AT) and the ACEI ramipril (RAM) regarding a protective role on these structures, as target organs in SHRs. [193] At the end of the experiment, SHRs receiving AT and SHRs receiving RAM (SHR-RAM) showed a similar control in blood pressure compared with untreated SHRs. However, SHR-RAM presented with a significant reduction in extracellular matrix expansion in the carotid glomus, autonomic ganglia and autonomic nerves. Moreover, the number of neurons was preserved with AT and even more with RAM compared with the untreated SHR group. TGF-β-1 and PAI-1 were increased in the carotid glomus and autonomic ganglia in SHRs and in SHRs receiving AT, whereas SHR-RAM showed a similar expression to the normotensive group (Wistar-Kyoto rats), indicating that RAM, but not AT, provided a significant protective role against structural changes in these structures caused by arterial hypertension in SHRs. This effect seems to be independent of blood pressure reduction. [194]

These structures were well preserved by an ACEI because permanent high blood pressure stimulates extracellular matrix expansion as a result of enhanced TGF-β-1 and PAI-1 production, through a mechanism regulated by the renin-angiotensin-aldosterone system. [193]

Previous studies have shown the existence of a local reninangiotensin-aldosterone system in the carotid glomus. [194] In agreement with this information, ACEIs could prevent fibrosis in barochemoreceptor structures observed in SHR by reducing local angiotensin II production. [194] The clinical importance of these data could be that the baroreflex attenuation in humans might be a consequence of atherosclerotic and/or hypertensive processes. [177,187,188]

Also the relationship between atherosclerosis and baroreflex sensitivity has been well documented in animal models. [55,63,194,195] Similar evidence in humans is both limited and indirect. [64] It is possible that the age-related baroreflex attenuation observed in humans may

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not be due to aging per se, but it may reflect atherosclerotic and/or hypertensive processes. [177,188,189]

Carotid barochemoreceptors are of utmost importance in the rapid adjustment of circulation and ventilation; the different degrees of involvement of these structures may explain various clinical responses. [196] These may encompass chronic hypertension, isolated systolic hypertension, blood pressure lability, postural lightheadedness and periodic orthostatic hypotension. [196] Elderly hypertensive patients with these relatively common conditions could be considered as a high-risk stroke group. [19,177]

Cooper et al [197] reported that the effect of both peripheral and central chemoreceptors on baroreflex function may contribute to promoting hypertension in patients with obstructive sleep apnea.Accordingly, Kario et al [196] investigated the clinical significance and mechanism of orthostatic blood pressure dysregulation in elderly hypertensive patients. They found that silent cerebrovascular disease is advanced in elderly patients with orthostatic hypertension.Elderly hypertensive patients with orthostatic hypertension or orthostatic hypotension may have an increased risk for developing cerebrovascular disease. In conclusion Severe carotid chemoreceptor damage exists in elderly patients who died from stroke and suffered from carotid atheromatosis, independently from aging and plaque type. The damage is plausibly related to a marked narrowing of their supplying arterioles as a consequence of hemodynamic (hypertension) and/or metabolic (diabetes, dyslipidemia) disturbances.

A high density of angiotensin II receptors was observed in the rat carotid body by in vitro autoradiography employing 125I- [SarÁ,IleÌ]-angiotensin II as radioligand. Displacement studies demonstrated that the receptors were of the AT1 subtype. [198]

As written above, the renin-angiotensin system has been shown to be responsible for ageing and hypertension which are the major risk factors for the development of cardiovascular and renal diseases.[197,199-202] We conducted an investigation [203] in which the the aim was to compare the effects of losartan, an angiotensin II type-1 receptor blocker, on systolic blood pressure, (SBP), and histopathologycal changes in the carotid body and autonomic lymphs in 14 spontaneously normotensive rats (WKY) They were divided into two groups, one of them treated with Losartan (n=7) and the other was a control group (n=7) not receving this drug. We also compared to spontaneously hypertensive rats (SHRs). As expected, at the end of the study the rats treated with losartan had a SBP of 105 ± 8.3 mm Hg, significantly less than controls (115 ± 8.1 mm Hg, p = 0.0375).The carotid body was found in the area fork or carotid bifurcation, formed by lobes compact traversed separated by connective tissue by numerous small blood vessels and nerve fibers blood (Figure 1). Parenchyma was formed by two cell types: primary cells or type I, large round nuclei and cells Hold or type II, elongated and located peripherally of the first (Figure 2). Lobes comprise the functional units of the structure they were best preserved in the group treated with losartan (Figure 3, A). Also, fibrous stroma was much more apparent in the control group, where the gap was increased with cell replacement and decreased in number (Figure 4, A). Clearly losartan treated rats showed glomus area more, a smaller thickness wall in the arterioles and a light periglómicas higher compared with the control group (Figures 3 and 4, A, B, C). All this made that the losartan group had a wall / lumen ratio significantly lower than controls in these vessels. These findings strongly suggest

atrophy of the structures analyzed. Through the increasing age is mainly linked with decreased arterial blood supply them and that the inhibition of AT1 receptor would a prominent role in the prevention of such alterations.

In conclusion, a severe carotid chemoreceptor damage does exist in old patients who died from stroke and suffering from carotid atheromatosis. The damage involved the glomic structures and of note, a ''culprit'' narrowing of the arterioles belonging to those structures was also observed. The clinical implications of these findings related to the development and/or worsening of all types of blood pressure and ventilatory disturbances in elderly patients are obvious. Hypertension could play aa very important role in the development of carotid body lesions -Beta blockade or Ramipril or Losartan could prevent morphologic and functional abnormalities

7. Final conclusions

This chapter was based on our experience in the pathology of the carotid arteries and barroreceptor as well as what exists in the international literature. The importance of knowing the biological phenomena that produces the formation of carotid atheromatous plaque is clearly emphasized. We also mentioned different plaque types (stable, unstable and calcified) and its correlation with diagnostic techniques. Concepts approached in the chapter offer the reader elements to enhance decision making in patients suffering carotid atheromatous disease. Additionally we emphasized the need to report on the origin and hemodynamic behavior of the carotid dolichoarteriopathies. Finally, we have highlighted the functions and the various pathological processes that can be observed in the carotid glomus.

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Author details

Ricardo Luis Beigelman, Andrés María Izaguirre, Francisco Azzato and José Milei

*Address all correspondence to: ininca@fmed.uba.ar

Instituto de Investigaciones Cardiológicas ''Prof. Dr. Alberto C. Taquini'' School of Medicine, University of Buenos Aires–CONICET, Buenos Aires, Argentina

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