Aus dem Zentrum der Rechtsmedizin der Johann Wolfgang Goethe Universität
Frankfurt am Main
Geschäftsführender Direktor Prof. Dr.med Hansjürgen Bratzke

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Inaugural-Dissertation zur Erlangung des Doktorgrades der Medizin des
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vorgelegt von Nathalie Alexandra Frickey
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Tag der mündlichen Prüfung: 13.06.2007

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Summary

Spontaneous carotid artery dissection (SCAD) is a major cause of stroke in young adults, yet its pathogenesis remains unclear. Hereditary connective tissue diseases, hormonal influences, sympathomimetic drugs or upper respiratory tract infections may predispose to dissection. Mechanical stress or minimal trauma may also act as a trigger. Various lesions of the arterial wall have been described in association with SCAD, but no prospective autopsy study to evaluate the presence of these lesions in normal controls was found. We performed a histologic evaluation of the carotid bifurcation and the aortic arch in an autopsy series to establish a baseline anatomy of the bifurcation and to determine whether similar lesions could be observed. In seven of 54 (12.96%) selected cases we observed isolated changes closely resembling those described for medionecrosis, fibromuscular dysplasia, mucoid degeneration and elastinolysis; and in one case, prior carotid artery dissection and coiling with a patent false lumen. Generally, vascular microanatomy in the carotid bifurcation can be highly variable. Lesions similar to those associated with spontaneous dissection are present in controls and appear non-specific for spontaneous dissection. They can be explained as reactive changes of smooth muscle cells (SMC) and the vascular wall in response to various stressors. Recent advances in vascular physiology are discussed to illustrate the concept of SMC phenotypic modulation. Forensic pathology can provide a large control population for extensive vascular analyses and further the understanding of normal and pathological vascular wall changes to help elucidate spontaneous arterial dissection.

Zusammenfassung

Spontane Carotisdissektionen (SCAD) sind einer der Hauptgründe für Schlaganfälle im jungen Erwachsenenalter, und doch ist über den Pathomechanismus dieser Erkrankung wenig bekannt. Erbliche Bindegewebserkrankungen, Hormoneinflüsse, sympathomimetische Drogen und virale Infektionen der oberen Atemwege können die Entstehung einer spontanen Dissektion begünstigen, ebenso wie mechanische Belastung oder minimale Traumata. Zahlreiche vaskuläre Läsionen werden im Zusammenhang mit SCAD beschrieben, jedoch gibt es bis heute keine prospektive Studie, die das Vorhandensein derartiger Veränderungen am Gesunden evaluiert. Wir haben eine histologische Untersuchung der Karotisbifurkation und des Aortenbogens anhand einer Kontrollpopulation aus dem Sektionsgut des Zentrums der Rechtsmedizin durchgeführt, um die normale Anatomie der Bifurkation zu beschreiben und festzustellen, ob Läsionen ähnlich der für spontane Dissektion beschriebenen auffindbar sind. In 7 von 54 Fällen (12,96%) wurden isolierte Läsionen oder Veränderungen gefunden, die wie Medionekrose, Fibromuskuläre Dysplasie, Mukoide Mediadegeneration oder Elastinolyse imponieren. In einem Fall fand sich sogar eine ältere Dissektion mit durchgängigem falschen Lumen und Invagination der dissezierten Media. Im allgemeinen ist die Histoanatomie der Karotisbifurkation hoch variabel. Läsionen ähnlich derer bei spontaner Dissektion finden sich in der Kontrollpopulation und sind wahrscheinlich unspezifisch für spontane Dissektion. Sie können als reaktive Veränderungen der Gefäßmuskelzellen und Gefäßwand auf diverse Stressfaktoren und äußere Einflüsse erklärt werden. Aktuelle Erkenntnisse aus der Gefäßphysiologie werden vorgestellt, um den Vorgang der Phänotyp-Modulation von Gefäßmuskelzellen zu illustrieren. Die Bedeutung der forensischen Medizin als Quelle für Kontrollfälle soll unterstrichen werden. Umfangreiche Analysen können so durchgeführt werden und das Verständnis über normale und pathologische Gefäßwände verbessern, um die Hintergründe der spontanen Dissektion besser begreifen zu können.

1. Introduction

Cardiovascular disease is one of the leading causes of death in the industrialized world. Because it affects so many lives in ways both personal and economical, vast amounts of time, money and effort have been invested in order to elucidate the mechanisms of atherosclerosis, hypertension, stroke and coronary artery disease. New therapies born from a better understanding of these diseases and risk factors have meant the difference between life and death for many. Research, generously funded and performed on a large scale, has provided not only new therapeutic strategies but also a wealth of data obtained from population studies, clinical trials and experimental work. Together, these begin to shed light on the complex interplay between vascular smooth muscle, endothelium, neural and humoral factors and inflammatory substances from the rest of the body.

Yet the immense scientific and public interest in atherosclerosis and associated disorders has a downside: most of the available data is interpreted only with regard to atherosclerotic disease, while other vascular diseases and disorders remain unexplored.

Cervical artery dissection is one among these, more particularly the phenomenon of spontaneous or “minimal-trauma” dissection, which is an important cause of stroke in adults and children, with sometimes devastating effects. The department of forensic medicine first was confronted with this subject after being approached with a request for an expert opinion in the case of a woman with cervical artery dissection (Case report). Research into this subject soon showed that while our knowledge of the epidemiology of this disease has evolved, owing in particular to the dedicated and intelligent work of Schievink, Mokri, Guillon, Giroud and many others, and technological advances have given us new diagnostic and therapeutic possibilities, current understanding of this

disease is reflected in the words most frequently found as an introduction to the matter:

“In spite of the increased recognition of spontaneous cervical artery dissections over the last decade, their cause and pathogenesis remain largely unknown.” [W.I. Schievink 1998]

Many groups have focused their attention on classifying histological alterations found in diseased vessels. Genetic analyses of particular connective tissue defects have been performed, and families with recurrent dissections followed over years. Yet the picture one finds is one of isolated facts and speculations rather an explanation of the vascular wall physiology, architecture and function needed to provide a background against which to examine and weigh the evidence accumulating step by step.

Collating the results of current anatomic, physiologic and genetic research into the vascular system with the epidemiology and clinical course of this disease should help to generate a cognitive map of the relationship between tissues, cell populations and mechanical factors influencing vascular development and disease and predisposing to spontaneous dissection.

1.1 Case report

In 1997, the following case was presented to the department of forensic medicine:

On December 21st, 1996 a middle-aged woman, slightly ill with the flu, left work at 6 a.m. after her night shift. During her ride home the driver following her observed her to be driving in zigzags and swerving back and forth over the separating line. She was then involved first in a minor accident, scraping by an

oncoming car while she was driving far to the left of the road. Without seeming to notice, she continued on her way and, ten minutes later, in a left-hand curve, collided with an oncoming car because she had been driving in the centre of the road.

Immediately after the accident, disorientation and retrograde amnesia were apparent, and the witness helping her out of the car noticed a pronounced weakness of the left arm and leg, and peculiar eye-rolling movements. She was incapable of standing unassisted. The airbag had been released, and the woman showed minor bruising on the right cheek. She was rapidly hospitalised upon becoming unconscious, recovered briefly during the transport but was comatose with left-sided hemiparesis upon arrival at the clinic. The initial CCT scan showed no visible skull or brain lesions, but a repeat scan several hours later revealed infarction of the right hemisphere, and an angiography revealed dissection and thrombosis of the right internal carotid artery. Following thrombectomy and vascular recanalization, the woman recovered but showed residual neurological impairment.

The insurance companies approached the institute of forensic medicine with the request for an expert opinion on the most probable sequence of events, i.e. whether the collision and trauma due to the airbag had caused the arterial dissection, or whether spontaneous carotid artery dissection with ophthalmoplegia or TIA was at the origin of both subsequent accidents. Reconstructing the event would be of major consequence for the involved insurance companies. During the research on this subject, information on the clinical manifestation and treatment of this disease was readily available, yet comparatively little seemed to be known about the circumstances of its occurrence or its possible underlying causes.

1.2 Aim of the study

Histological assessment of dissection of the carotid artery is hampered by the fact that the disease is seldom lethal, and rarely necessitates surgical intervention requiring removal of the injured vessel part. Most existing histological studies on this subject are based on few cases in which the disease was fatal and clinical or post-mortem diagnosis allowed tissue samples to be taken. Few articles mention the presence of cervical vascular dissections found during autopsy, and most are case reports, anecdotal findings or retrospective evaluations of post-mortem diagnoses.

Aortic dissection has been more extensively studied, but occurs with different disease patterns and samples are more often obtained because of reconstructive surgery. To our knowledge, there has been no systematic prospective histological examination of cervical arteries to elucidate the relationship between vascular wall pattern alterations and the possible occurrence of spontaneous cervical artery dissection.

The histological changes most often described in association with SCAD are mucoid degeneration, cystic medionecrosis, fibromuscular dysplasia and focal elastinolysis; these may occur alone or in combination and are most often described for elastic arteries (aorta). The terms are purely descriptive and give no information as to a possible underlying disorder leading to vascular dissection. A systematic, prospective histological study of carotid and aortic samples was performed in order to a) evaluate the normal anatomy of the carotid bifurcation as a transitional zone between elastic and muscular arteries and b) to search for changes resembling the abovementioned lesions. Their presence in otherwise normal vessels would indicate a non-specific nature and provide further incentive to study the mechanisms that generate these lesions and predispose to spontaneous dissection.

2. Spontaneous cervical artery dissection

Dissection of the extracranial internal carotid artery is increasingly recognized as one of the major causes of ischemic stroke in adults younger than fifty (1, 2, 3, 4). Spontaneous carotid artery dissection (SCAD) is evoked whenever there is no relationship to trauma to account for the dissection. It occurs mainly in previously healthy adults in their fourth decade in the extracranial internal carotid artery, although combined dissections including the vertebral arteries exist. Local signs and symptoms of dissection include headache, neck pain, Horner syndrome, pulsatile tinnitus and cranial nerve palsies, as well as transient or permanent ischemia of the brain or retina, although some cases remain asymptomatic.

2.1 Cervical artery dissection

Morphology

Dissection of an elastic or muscular artery is the manifestation of a division within the vascular media creating an enclosed or patent blood-filled false lumen parallel to the original lumen that is often obstructed by the spreading intramural hematoma. The hemorrhage can rupture back through the intima and create the pathognomonic double-barreled vessel with a true and false lumen. The plane of dissection nearly always lies in the tunica media, either joined per continuitatem to a tear in the intima, or originating de-novo within the media, in which case a connection to intramural vasa vasorum is postulated and sometimes found. The origin of the intramural hematoma is considered to be due either to penetration of the media following an intimal tear, or through direct hemorrhage from the vasa vasorum into damaged media zones (5).

The internal carotid artery (ICA) at the most common site of dissection just above the bifurcation is mobile and less firmly anchored than at the origin or intracranial sites. This area is more liable to endure stretching and tearing during movement. Perivascular hemorrhage is infrequent in cervical artery dissection (CAD); although in a few instances there can be limited rupture of pseudoaneurysms into the surrounding tissues.

Symptoms

Subadventitial dissection results in an expanding hematoma with symptoms due to nerve fiber compression or ischemia such as Horner Syndrome or cerebral nerve palsy. Mounting intramural pressure can disrupt the arterial wall and cause perivascular hemorrhage.

Subintimal dissection leads to a narrowing of the lumen and ischemic symptoms; infarction occurs when the arterial lumen is occluded or because of thrombembolism after damaged endothelial cells release procoagulant factors into the blood stream. Clinical symptoms are usually caused either by embolization of thrombi (6), or by nerve compression or distension (7).

Location of dissection

Cervical artery dissection happens most frequently in the cervical and pharyngeal part of the extracranial internal carotid artery and often in the vertebral artery. The dissection is frequently situated in the distal segments two centimeters above the carotid sinus and the dissection plane usually lies in the media or in the subadventitial plane. In most cases, an intimal tear seems to be the entrance point for the diverted bloodstream, but not in all. In the internal carotid, the hematoma usually extends to the pars petrosa, where it ends abruptly.

2.2 Traumatic cervical artery dissection

Spontaneous dissection is sometimes referred to as “minimal-trauma” dissection, but this is a misleading term, since in many cases no originating trauma can be obtained from the patient's history. The differentiation between traumatic and spontaneous dissection is probably artificial and poorly reflects the continuum of cases (8). Traumatic cervical artery dissection (TCAD) occurs most frequently in the internal carotid artery due to its non-fixed position allowing it freedom of movement, and is clearly linked to a precipitating, often violent event. Deceleration and rotational trauma, as during falls or motor vehicle accidents, are particularly apt to cause TCAD in the carotid and vertebral arteries, although other mechanisms have been implicated as well, as for instance “out-of-position” impact of inflating airbags, strangulation, hanging and chiropractic manipulation (9,10, 10a,11,12). TCAD occurs in a comparatively young population due to the greater prevalence of sport-associated violent falls and motor vehicle accidents in young people. Despite their relative youth and health, patients with traumatic dissection have a poorer prognosis than those with spontaneous dissection, since the originating violent trauma often causes concomitant, severely debilitating and even fatal injuries (13).

2.3 Epidemiology of SCAD and SCAD-associated stroke

Spontaneous dissection of the internal carotid artery has been reported with increasing frequency since 1954, reflecting an increasing familiarization with this disease as well as better diagnostic tools. Population studies performed in Minnesota and Dijon have provided a base of knowledge about the incidence, epidemiology and lethality of SCAD (14,15,16)

2.3.1 Incidence of SCAD in adults and young people

In European and North American study populations, SCAD showed an overall incidence of 2.6 – 2.9/100,000 p.a. The incidence for people above age 30 was 3.5/100,000 p.a. (17,15). Cervical artery dissection also occurs in children and adolescents <18, the Minnesota study describing it in 6.8% of the study group (1). At this age, intracerebral dissection is more frequent than in adults and accounts for 30% of cases but only 10% in the adult patients, and there seems to be a strong male preponderance (3).

2.3.2 Dissection-associated stroke

Dissection-related stroke has been described in up to 52% of cases of SCAD in the general population (18). Morbidity from carotid artery dissection varies in severity from transient neurological deficit to permanent deficit and death. In contrast to extracranial carotid dissection, which has a high recovery rate (15), intracranial internal carotid artery dissection is associated with a 75% mortality rate. The male-to-female ratio for carotid dissection is reported as 1.5:1. Up to one-fifth of all ischemic strokes occurring before age 45 are due to cervical artery dissection, the internal carotid artery (ICA) being the most commonly affected (19, 20). Patients with stroke due to carotid artery dissection were found to be more likely to have suffered from upper respiratory tract infection one week prior to the occurrence than patients with non-SCAD-associated stroke in a case-control study (21). SCAD accounted for 2.5% of strokes in adults <45 years, the figures increasing to 10% of strokes in adults <30, and 30% in children and adolescents <18. Despite its usually benign manifestation and prognosis, SCAD in some cases can have disastrous consequences, particularly if the diagnosis is formed too late. The true incidence of SCAD is probably higher than reported, since clinically silent dissections or those with minor, transient symptoms may escape detection altogether while the more severe forms with large infarction

may not be evaluated in the acute phase (14). Furthermore, the incidence in the elderly on whom MRI or angiography are less frequently performed for stroke is unknown.

2.4 Symptoms and clinical presentation

MOKRI described the manifestations and time course of symptoms in a large group of SCAD patients (14). The initial manifestation was pain in 86% of cases, and headache was present during the disease in 92% (mainly focal unilateral anterior or periorbital headache). Focal ischemic symptoms occurred in 67% (TIA; stroke), often with a delay of minutes to 11 days following the initial headache; oculosympathetic paresis (Horner Syndrome) was the third most common manifestation with 58% and was also delayed by 1 hour to 3 days after the onset of headache. Subjective bruits ipsilateral to the dissection were reported in 50% of cases, followed by light-headedness, neck pain, syncope, scalp tenderness and amaurosis fugax as less frequent manifestations.

Depending on the dissection plane, the presenting signs may vary significantly. Subintimal dissection often manifests with ischemic neurological symptoms (TIA; stroke) because the hematoma causes obstruction of the lumen, while subadventitial dissection permits the hematoma to expand into the surrounding tissue. In the latter case, symptoms are the result of direct compression or distension of local nerves (neck pain) and/or sympathetic plexus (Horner syndrome); or are due to the interruption of blood flow through nutrient arteries, resulting in various cerebral nerve palsies (oculomotor, hypoglossal) (22, 23, 24). Abrupt, severe ipsilateral neck and head pain as well as pulsatile bruit and tinnitus are typical manifestations common to both forms of dissection (25). The more serious course is when the patient presents with massive neurological deficits and rapidly develops ischemic stroke. This is usually due to subintimal dissection with lumen occlusion, although thromboembolic mechanisms also play

an important role. The injured vessel wall initiates coagulation, and the ensuing thrombus can occlude the entire lumen or produce microthrombi, which embolize to the cerebral circulatory system.

The most common localization of ischemia is the territory of the middle cerebral artery in the case of internal carotid dissection, but bulbar and pontine infarctions can and do occur in cases of vertebral artery dissection and can present with occipital pain. The most benign and most severe cases of dissection may escape diagnosis so the clinical picture is biased (14, 25). Rupture and hemorrhage are rare in SCAD, and occur more frequently in young adults and adolescents, where however it is associated mainly with dissections of intracranial arteries, which are relatively more frequent in this age group (30% versus 10% in adults) (1).

2.5 Diagnosis

Greater awareness of this disease is important to ensure prompt diagnosis and targeted treatment in order to reduce the risk of deleterious consequences. Suspicion of SCAD should follow clinical presentation with typical signs or complaints (see 3.4.1). Symptoms may be transient and or minimal, so that patients never consult a physician and remain unaware of their disease. In these cases, the course of SCAD is usually benign and does not require treatment. In cases with more severe presentations, however, SCAD needs to be suspected before the right examinations can be performed. Imaging (see below) is the method of choice to validate the clinical diagnosis; duplex ultrasound is a non-invasive method that can confirm SCAD in many cases.

In general, when patients present with typical signs, such as abrupt neck and head pain, pulsatile bruit, tinnitus and focal neurological signs or Horner syndrome, suspicion is high and the correct diagnosis is more likely, despite the

fact that targeted treatment is often delayed (24). Atypical or monosymptomatic presentation or delayed onset of symptoms can be misleading and even entail treatment for a completely different disease. Since stroke can be delayed by hours or even days following dissection, early diagnosis and follow-up observations are of paramount importance in detecting the development of thrombi or progressive luminal occlusion. Long-term follow-up is also useful in detecting the resolution or persistence of aneurysms, thrombi, vascular malformations and stenoses.

2.6 Imaging techniques

Contrast arteriography is still the gold standard for the diagnosis of traumatic and spontaneous CAD, but the past years have seen a rise in diagnostic imaging methods, so that today we dispose of an impressive array of tools to detect and follow-up CAD. Invasive or non-invasive diagnostic steps should be considered in any of the following situations: neurological findings incompatible with bland CCT, mono- or hemiparesis with normal mental status, signs or history of cervical or cranial trauma or manipulation with abnormal neurological symptoms.

2.6.1 Contrast arteriography

Angiographic or digital subtraction angiography (DSA) findings in SCAD include luminal stenosis (70%), abrupt lumen reconstitution at the carotid canal (48%), aneurysms (37%), intimal flaps (35%), slow ICA flow (22%), luminal occlusion (17%) and distal embolic occlusion (11%). The pathognomonic double lumen is present in only 4% of cases (25). Atherosclerosis is rare in cervical artery dissection. Other findings include the “string sign” – a long tapered narrowing of the vessel (intramural hematoma); segmental stenosis or occlusion; and the “string-of-beads” appearance of muscular arteries with fibromuscular dysplasia (FMD).

2.6.2 Computed tomography and digital imaging

Digital imaging techniques are establishing themselves as sensitive tools in the diagnostic process, particularly when standard angiography is contraindicated or cannot be performed. A native CT scan with axial slices through the dissected artery in general shows close agreement with arteriography, but can also detect mural thickening (intramural hematoma) in cases with “normal” arteriography. CT can play an important role in diagnosis and follow-up (26).

2.6.3 Magnetic resonance imaging

Magnetic resonance imaging (MRI) or arteriography with time-of-flight imaging (MR-TOF), 2D or 3D arrays and phase-contrast display shows sensitivity and specifity approaching that of standard angiography, and in combination these examinations allow a detection of SCAD with nearly 100% accuracy. In conventional MRI signs of CAD are eccentric tapered stenoses or luminal narrowing. Occlusion of the ICA can be demonstrated in <20%, dissecting aneurysm in <10%, often with intramural hematoma (27). In contrast to arteriography, MRI can prove dissection by showing the mural hematoma. It can also show the degree of wall expansion and the relationship with surrounding structures. The hematoma in dissection appears as a crescent-shaped hyperintense signal on T1- and T2-weighted images. MRI is more helpful in detecting extracranial dissections than intracranial dissections. The limitations of MRI are the difficulty of grading stenoses and in assessing the longitudinal extension of dissection, because low blood-flow velocities distal to high-grade stenoses may cause flow-related enhancement. MRI is less sensitive than arteriography in detecting arteriopathies such as fibromuscular dysplasia and tortuosities.

2.6.4 Magnetic resonance angiography

Magnetic resonance angiography (MRA) is a noninvasive tool that allows multiplanar and multidirectional vessel imaging and projection without the need for an injectable contrast agent; it is performed easily as part of an MRI study. The combination of MRI and MRA is more reliable in detecting dissection than either examination alone. MRA is good at detecting irregularities, taperings and aneurysmal dilations in dissected vessels; but can give the appearance of vessel widening when the axial spin-echo images at the level of the dissection show the high signal surrounding the narrowed vascular lumen.

2.6.5 Ultrasound

Transcranial Doppler (TCD) and color-coded duplex sonography, combining ultrasound and flow-velocity measurements are ideal as screening and follow-up examination, especially in patients with counter-indications for invasive procedures. Duplex scanning combines Doppler and ultrasound measurements and being fast, convenient, noninvasive, and highly sensitive can be performed early to detect the characteristic pattern of dissection. Compared to an unaffected vessel, the doppler signal of a dissected proximal internal carotid artery appears as a high-resistance wave form, with decreased velocity and altered resistance index, two separate frequency curves on spectrum analysis, and temporal fluctuation of signals or a short systolic flow signal.

The ultrasound image can display a double lumen with intimal flap, minimal atherosclerotic changes in the arterial wall, occlusion of the arterial lumen, narrowed lumen with intima overlying an intramural thrombus, or the characteristic long tapered stenosis. It is highly sensitive in detecting significant vessel obstruction. The limitations of duplex scanning include poor performance in scanning the distal internal carotid artery, detecting emboli, and evaluating

intracranial arteries. In addition, the ultrasound component has a low sensitivity for dissections that cause low-grade stenoses only.

Transcranial Doppler is useful and effective in detecting emboli in patients at risk for stroke and to monitor therapy success when anticoagulation is performed (28). TCD can detect intracranial arterial abnormalities, provide information on collateral flow, and follow microemboli in the middle cerebral artery distal to a carotid dissection. Visible emboli on TCD correlate significantly with stroke, as does a high-resistance Doppler signal (6).

2.7 Treatment, prognosis and follow-up

In most patients with extracranial carotid artery dissection, symptoms and morphological vascular changes spontaneously resolve within a few months, but in some cases there may be lasting neurological deficits, especially if the patient initially presented with stroke. Patients manifesting with focal or extensive ischemic neurological symptoms carry a far greater risk of suffering a stroke, and these patients require close observation and antithrombotic treatment, and some will need surgery.

2.7.1 Management of suspected or proven SCAD

Surveillance

Once the diagnosis has been made, there are several therapeutic options depending on the severity of presentation and accompanying risk factors of the patient. There are no standard therapy guidelines and treatment is decided on a case-by-case basis. In silent or oligosymptomatic forms, especially if there is sufficient blood flow or lumen restitution after downstream intimal rupture, observation is considered sufficient. Spontaneous resolution is frequent and follow-up can detect persisting stenosis or aneurysm formation.

Anticoagulation

In many cases, the patient is put on an antithrombotic regime with heparin or anti-platelet drugs unless there are contraindications. In patients with persisting aneurysm or thrombotic tendency, locoregional thrombolysis or anticoagulation for several months can be considered, again barring contraindications.
A trial of anti-platelet medication has been performed in several centers, but it is unclear whether this affected the outcome in any way. When the presentation is benign, “watch-and-wait” seems to be as effective as medical intervention.

Surgical intervention

In cases with ischemic symptoms, surgical intervention is warranted. There have been several studies comparing the effectiveness and outcome of various surgical procedures but the results are equivocal. Again, case-by-case evaluation and tailored intervention seem to be the bottom line of recommendations. The surgeon faces a choice of open or endovascular treatment, and in some cases good results have been achieved with temporal- to middle-cerebral-artery anastomoses to alleviate ischemic symptoms in ICAD, leaving the ICA untouched until the dissection had resolved spontaneously. In general, the more serious cases profit most from surgical intervention, and a better understanding of the pathogenesis and progression of this disease will no doubt be instrumental in the further mapping of indications.

Follow-up

Regular follow-up examinations should be scheduled to monitor resolution or persistence of stenoses, aneurysms or thrombi and to initiate anticoagulation or surgery if symptoms persist. Familial screening and regular controls are warranted in cases of familial dissecting aneurysms.

2.7.2 Prognosis and recurrence

Intracranial carotid artery dissection is more frequent in younger people and usually entails a poorer outcome than in adults (1,27). Recurrence rates for spontaneous dissection are low, except for familial dissecting aneurysms. In one study (29), recurrence patterns showed a bimodal distribution, with an early recurrence within the first month of nearly 8%, and late recurrence after more than one year with an annual risk of 1% and a cumulative recurrence risk of 11.9% in 10 years. Younger patients had a higher risk for redissection (30).

2.8 Familial SCAD

There is one type of patients with a different profile of SCAD occurrence and recurrence. A family history of SCAD entails a much higher risk for SCAD in the individual, and the recurrence risk is elevated as well (31). Familial SCAD is associated with earlier onset and more severe manifestations (early stroke, multivessel dissection) than non-familial SCAD. A positive family history should raise the suspicion index, and surgical intervention is more often necessary in concerned individuals. A positive family history of SCAD has been described for 2% – 18% of patients with cervical artery dissection (30). In several cases, hereditary factors such as connective tissue diseases or neural crest defects have been suspected or detected in families with frequent SCAD.

2.9 Associated diseases and morphological changes

In connective tissue diseases, the underlying pathology reflects in abnormal formation or metabolism of elastic and collagen fibers, and manifestations include spontaneous arterial dissection but also skin and eye defects (cutis

hyperelastica, congenital lens luxation) and a typical habitus. Oligosymptomatic or atypical manifestation of these diseases may explain some instances of SCAD, but in many cases there is no evidence of connective tissue disease.

2.9.1 Hereditary connective tissue disease

There is a clear association between SCAD and Marfan syndrome, Ehlers-Danlos syndrome type IV, alpha-1-antitrypsin deficiency (32) and cardiovascular malformation. Familial dissecting aneurysm (30) and collagen defects are associated with an elevated risk for SCAD. In some cases, patients with SCAD were found to have a “forme fruste” of osteogenesis imperfecta (33), in others, dermal connective tissue abnormalities resembling those found in Ehlers-Danlos Syndrome type II and III were found (34).

2.9.2 Histological vascular wall changes

These are changes and combinations of changes in the vascular wall that have had several names before. Medionecrosis Erdheim-Gsell, segmental mediolytic arteriitis, and cystic medial degeneration all served to describe histologic patterns of alteration found in cases of SCAD or aortic dissection.

Cystic medial necrosis

The histopathological criteria for cystic medial necrosis (CMN) are a localized increase in pale ground substance in the media accompanied by loss of smooth muscle cells and fragmentation of elastic fibers. CMN is the most characteristic lesion in Marfan’s Syndrome and has been described in cases of SCAD, however it is unspecific in nature and can be found in 2% of general autopsy populations (35).

Mucoid media degeneration

LEU coins the term mucoid media degeneration to replace “segmental mediolytic arteriitis” used before to describe lesions in dissected muscular arteries. Histologically, mucoid media degeneration is characterized by segmental accumulations of mucoid ground substance in the media accompanied by destruction of the internal elastic lamina. Within the vessel wall of elastic arteries, the elastic fibers are not destroyed but atrophied and pushed aside by accumulations of mucoid ground substance (36). Vessels with mucoid degeneration of the media are much more likely to undergo dissection rather than aneurysmatic distension. Possible causes discussed for this vascular wall damage are abnormal mechanical stress, hypoxia, stenoses of the vasa vasorum, and weakness of the connective tissues, adrenaline-necroses induced by stress, nicotine abuse, collagen destruction and infection. On one hand, exogenous toxins seem to play a role in the development of this lesion, yet the segmental involvement appears more typical of autoimmunopathic processes (37).

Fibromuscular dysplasia

In 1987 Lüscher et al. (38) described a very similar lesion, which they called fibromuscular dysplasia (FMD). It is described as “a vasculopathy of uncertain etiology, histologically characterized by fibrous tissue proliferation, smooth muscle cell hyperplasia and elastic fiber destruction, alternating with segments of mural thinning. […] Arterial involvement is not diffuse but segmental with a predisposition for long unbranched segments of medium-sized muscular arteries, such as the renal, internal carotid, subclavian, vertebral, visceral and iliac arteries”. Histologically, areas of mural thickening alternating with segments of thinning characterized FMD. Thickened areas were composed of a disorganized proliferation of smooth muscle cells and fibroblasts; elastic tissue was in disarray and usually decreased in amount while mucoid ground substance was prominent. FMD usually spares the proximal portion of the internal carotid artery.

More than 80% of cases appear in women, the majority being in their 5^{th} – 7^{th} decade (38). LIE (39) also claims that segmental mediolytic arteritis is a misnomer since the lesions it refers to are noninflammatory dysplastic changes, and states that the lesions described are identical to those observed in fibromuscular dysplasia of muscular arteries. Both CMN and FMD have been associated with Ehlers-Danlos-Syndrome, Turner Syndrome, aortic coarctation, autosomal dominant polycystic kidney disease (CMN), and alpha1-antitrypsin deficiency (FMD) as well as collagen type III gene mutations (FMD). Angiographically present in 15%- 20% of SCAD patients as compared to less than 1% in the general population (35), FMD may localize to different vessels and is implied in the pathogenesis of multiple artery dissection involving cervical and renal, thoracic and splanchnic vessels. In a clinicopathological series of 20,244 autopsies, FMD was found only in four cases (0.02%) (40,41).

2.9.3 Recent viral infection

Recent or acute viral upper respiratory tract infection is significantly associated with SCAD, and in northern America (temperate climate) a significant circannual periodicity in the occurrence of SCAD has been demonstrated, further arguing the case for external trigger factors (42,43,44).

2.9.4 Associated factors

Several other factors have been described in association with SCAD without a clear causal relationship.

Hormonal changes and migraine headache

Cases of SCAD and spontaneous coronary artery dissection have also been reported in connection with pregnancy (45), use of hormonal contraceptives (46,41) or migraine headache (47,48). Hormonal influences on the vessel wall have been described which might predispose to dissection of muscular arteries.

Pregnancy has been shown to alter the collagen synthesis and organization in the aorta, and there is a rapid post-partum breakdown of accumulated collagen in the uterus, together with evidence of increased collagen turnover in all blood vessels due to the increased cardiac output and altered hormonal status (14,44).

Hypertension

Hypertension has been found in association with SCAD (47% of subjects in one study) (14) though any possible causal relation remains unclear.

Sympathomimetic drugs and smoking

There are case reports of cocaine and metamphetamine-associated aortic dissection (49,50), but so far no relation to carotid dissection has been shown. Since cocaine seems to trigger vasculitis in some patients it could easily predispose to carotid artery dissection, too. Nicotine abuse has been described in SCAD patients (47% smokers) but the pathomechanism remains unclear, possibly adrenaline necroses are responsible for a weakened vessel wall (14).

3. Vascular development and physiology

Since arterial dissection seems to be the result of reactive smooth muscle cell (SMC) and matrix changes, the origins and interactions of these tissues need to be better understood. A lot of knowledge has been gained in the past years and will be sketched here.

3.1 Vascular development and origins of smooth muscle cells

Embryonic vascular growth

Vasculogenesis describes the creation of primitive sinuses from angioblasts, while angiogenesis refers to the migration and proliferation of endothelial cells from pre-existing vessels. Angiogenesis is an ongoing process in the adult organism, while vasculogenesis is a term strictly applicable only during embryonic and fetal growth.

In the beginning of the third gestational week isolated hemangioblasts displaying endothelial and hematopoietic immune markers appear. They coalesce to form cords and clusters that differentiate into megaloblasts (precursors of red blood cells) and angioblasts. As soon as these endothelial progenitors are initiated, they become mobile and form primitive endothelial sinuses, which eventually connect with the primordial heart and form the first circulatory system by the end of the third gestational week.

As the embryo develops, the primary network expands to incorporate the cardiac sac and the paired aortae with their branchial arches, which undergo profound rearrangement, fusing and twisting to create the cervicocephalic and thoracic arteries. During this process, much of the embryonal vascular system disappears. Its remnants form the foetal and later the adult circulatory system.

The common and external carotid arteries grow from the ventral aorta, the internal carotid is a leftover from the dorsal aortae while the carotid bifurcation itself originates from the branchial arch artery III (51,52).

Smooth muscle cell precursors

During the growth phase, medial smooth muscle precursor cells are recruited via chemotactic factors[1] from the splanchnic mesoderm, mesenchymal endothelial cells, subendothelial SMC of the parent vessel and neural crest tissue in the cervicocephalic and pericardial arteries. These medial SMC precursors surround the endothelial sinuses and the primitive aorta and develop into venous or arterial media depending on the presence of activating growth factors (PDGF, TGF-ß and VEGF) from the endothelium and surrounding tissue as well as certain coagulation factors (TF, F V) from the blood. The establishment of SMC around endothelial cells coincides with the initiation of blood flow and an increase in blood pressure within the endothelial tube. Mechanical forces play an important role in the recruitment and differentiation of SMC during arterialization (53,54,55,56).

Differentiation markers

Smooth-muscle alpha-actin, an early SMC differentiation marker, is not expressed in the primitive endothelial cells and allows the study of SMC lineages during vascular development. Late differentiation markers such as SM22, calponin, h-caldesmon and SM myosin become more pronounced as the SMC matures. Analyses of the location of differentiation markers in the adult vessel wall show that subintimal SMC remain less differentiated than the middle and subadventitial SMC and show a random or clustered arrangement unlike the circumferential alignment of the latter (55,56).

[1] PDGF, VEGF, TGF-ß1, bFGF, angiopoietins, integrins and coagulation factors

Adult vessels

The differentiation of vessels into elastic or muscular arteries is poorly understood and probably is due to the interplay of regulating genes, cell origin and functional demands on the vessel wall. It appears that substantial portions of the vascular system are determined, although not fully formed, by birth. In large vessels, the numbers of layers of smooth muscle seem to be predetermined and at parturition, most arteries seem to have developed their adult number of layers. Consecutive medial thickening is due to increase of cell number, cell mass and production of connective tissue but not to increase in the number of layers. Subadventitial SMC with fetal differentiation markers and endothelial-cell derived SMC have the ability to migrate across the vessel wall and can be recruited for vessel wall repair (52,55).

3.2 Smooth muscle cells, endothelial cells and vessel wall matrix proteins

3.2.1 Vascular smooth muscle cells (SMC)

The vessel wall depends on the SMC for contractility, nutrient absorption and matrix formation. Different phenotypes of SMC can be found within the arterial wall.

SMC phenotypic modulation

During the recruitment phase of embryonic development, the smooth muscle cell precursors are autonomous (they express their own growth stimulator (bFGF) released from intracellular stores), mobile, and migrate towards the source of extracellular growth factors where they produce large amounts of extracellular matrix. During maturation, there is a change in RNA secretion and protein expression and the SMC undergo a transition towards a quiescent, contractile phenotype traced most consistently through the smooth-muscle alpha-actin marker. Contractile SMC appear elongated, are firmly anchored in organized

matrix structures and express markers such as smooth muscle alpha-actin, myosin heavy chain, desmin and tropomyosin (57). These cells are responsible for normal vascular tone, vasodilatation and -contraction and the linkage with nervous fibers.

Even in the adult vessel, however, some SMC retain or can revert to the secretory, mobile profile and are easily recruited for injury repair or vascular wall adaptation and modulation (58). These cells show a remarkable increase in secretory abilities, and reduce their anchoring by changing into spindle-shaped, non-digitating cells and secreting elastase and matrix metalloproteinases (MMP) into the surrounding matrix. Under the correct in vitro and also in vivo circumstances, smooth muscle cells are able to convert from the synthetic to the contractile phenotype and vice versa (59). The acquisition of the secretory profile is accompanied by a re-expression of embryonic gene patterns and markers and by an increased rate of apoptosis (54,55,60). There are two possible explanations for this behavior: some postulate the presence in the vascular wall of two or even more distinct subtypes of smooth muscle cells (61), possibly related to different embryonal lineages (62); others are of the opinion that various external influences such as matrix composition, growth factors, cell-to-cell contacts, neural input and mitogens from the endothelium and blood determine the SMC phenotype (63); even, that there is an entire continuum of SMC modulated by matrix proteins explaining the cellular diversity (64). There seem to be several pathways to activation, and modulation to the secretory phenotype is not necessarily accompanied by proliferation.

Vascular environment and SMC shift

In order to disengage from the matrix, activated SMC alter their cytoskeletal proteins and intercellular contacts, and then secrete proteinases to disrupt the surrounding matrix, which is replenished and stabilized by the remaining quiescent SMC. Once the activated SMC have disengaged from the matrix, they provide their own proliferative/secretory autocrine feedback loop while

remodeling the vessel walls. Chemotactic signals from injured endothelial cells and monocytes attract them to lesion sites. When the balance between proliferation and restraint is upset, exaggerated growth can lead to medial hyperplasia, hypertrophy and intimal hyperplasia, increasing blood pressure through reduction of the lumen. The phenomenon of post-angioplasty re-stenosis exemplifies the setting in which dedifferentiated SMC overwhelm the restraining faculties of the media and produce an excessive reaction to injury.

3.2.2 Endothelial cells

In health, the vascular endothelium forms a multifunctional interface between the circulating blood and the tissues and organs. It acts as a selectively permeable membrane for macromolecules and constitutes a nonthrombogenic and nonadhesive dynamic container that actively maintains blood fluidity. It is also a metabolically active endocrine organ, secreting mediators essential to rheologic homeostasis. These include vasodilators, vasoconstrictors, pro-and antithrombotic factors, fibrinolytic activators and inhibitors, adhesion molecules and cytokines. Besides their influence on the cardiovascular system, endothelial cells (EC) represent an important part of the immune system with a pivotal role in the initiation and development of inflammatory response. Within the vascular wall, EC act as SMC organizers and serve as interface between blood and medial SMC during vascular growth (52). They share the potential dimorphism of SMC and are modulated by intercellular contacts (gap, adherens and nexus junctions) (65), matrix binding factors, blood, medial SMC and mechanic and rheologic factors. As in SMC, the metamorphosis from quiescent to mobile state is effected through a reorganization of the cytoskeleton (stress fibers, alpha-actin, vinculin) and cellular contacts (66).

Shear stress and EC secretory profile

In a high-shear environment, such as the carotid divider wall, the EC aggregate in a smooth layer and are oval or polygonal in shape. The intercellular junctions

are tight around the luminal and abluminal cell rim and the secretory profile of the endothelial cell tends to the non-proliferative, antithrombotic and anti-inflammatory (67). In regions of low or oscillating shear stress the endothelial cells disband and lose their regular shape and alignment. Gaps appear between individual cells, and the profile is now pro-thrombotic, pro-proliferative and pro-inflammatory, allowing the passage of low-density lipoprotein (LDL) and lipopolysaccharides (LPS) into the media, attracting monocytes and lymphocytes as well as releasing thrombogenic factors into the blood stream (68,65).

The endothelial monolayer is also vulnerable to circulating serum factors created at remote injury sites. EC have been implicated as key intermediaries in the response to endotoxemia, ischemia/reperfusion, sepsis and hemorrhagic shock (69). The behavioral alteration of EC entails one of medial smooth muscle cells also; they are activated and begin a proliferative and secretory activity similar to that observed in wound repair. The biochemical and physiological balance of the vessel wall is profoundly altered. LDLs accumulate at the site of disturbance, and are taken up by local macrophages. These accumulations eventually form fatty streaks, and later atheroma. The atheroprotective effect of shear stress is mediated by the upregulation of superoxide dismutase and nitric oxide synthase in the EC, blocking the apoptosis-inducing caspase which is activated by extracellular oxygen radicals, oxidized LDL and TNF-alpha (70). Shear stress is a central protective cellular mechanism to preserve endothelial integrity (71).

Endothelial cell junctions

Adhesion of endothelial cells to one another and to the extracellular matrix proteins is mediated by various surface receptors such as cadherins, integrins, immunoglobulins and proteoglycans. Besides mechanical attachment, most adhesive receptors interact with cytoskeletal and cytoplasmic molecules and contribute to the regulation of cell morphology and signaling. Two classical adhesion complexes are expressed in the EC: adherens junction (AJ) and tight junction (TJ). The latter are located apically in a restricted band-like pattern and

regulate endothelial permeability. Adherens junctions are thought to be communication centers necessary for transducing signals between neighboring cells. In the EC, kinases and signaling molecules are concentrated at intercellular contacts and in some cases are directly associated with intracellular molecule complexes or cytoskeletal proteins. Adherens junctions have an endothelial-specific transmembrane component called vascular endothelial cadherin (VE-cadherin) that inhibits cell migration and proliferation and restricts paracellular permeability. The bioactivity of cadherin is linked to its capacity to bind to intracellular catenins or actin cytoskeleton fibers.

3.2.3 Vascular wall matrix proteins

Matrix protein action on SMC

The vascular wall matrix comprises a large number of proteins, most notably collagen, elastin and proteoglykans. A more detailed analysis of matrix composition shows a highly complex and variable matrix layout, with protein subgroups such as desmin, fibronectin, vitronectin and laminin, which affect SMC activity. Elastin, collagen IV, desmin and laminin have a growth-inhibiting influence on SMC and support the well-differentiated contractile phenotype (72), while fibronectin in certain circumstances and vitronectin in general support a proliferative behavior and synthetic transformation in adjacent SMC. Collagen VIII plays an intermediate role, important during vascular repair and remodeling, by promoting both attachment and chemotaxis in medial SMC, and stimulating MMP synthesis in intimal SMC via integrin receptors (66). Collagen I slows proliferation but supports synthetic-type SMC; it appears that synthetic-state SMC can exhibit differential biosynthetic activity dependent on the matrix environment (73).

Elastases and Matrix Metalloproteinases

There are several types of matrix-degrading enzymes in the vascular wall and endothelium. Most important for vessel wall remodeling during development and

in wall repair are elastases and a group of collagenases known as matrix metalloproteinases. Among these, MMP-2 and MMP-9 are foremost in the degradation of collagen IV and other basement membrane components. MMP activity is tightly controlled by several subtypes of tissue inhibitors of metalloproteinases (TIMP). TIMP-1 inhibits all activated MMP, preferentially MMP-9, which is responsible for invasive cell migration. The substrates of MMP-2 and MMP-9 include collagen I and IV, fibronectin, laminin and vitronectin. MMP-14, dependent on TIMP-2, activates MMP-2, insuring a close control mechanism to protect the matrix from destruction (74,75). Elastases and MMP are part of the proteinases secreted by activated SMC in order to disengage from the cellular network and may play a role in weakening the vessel wall in dissection (76).

Repartition of intercellular junctions

Stress and strain in the vessel wall are not distributed uniformly and seem to affect the distribution patterns of intercellular junctions. In studies performed on rats, the inner elastic lamellae were thicker than the exterior lamellae in adults. SMC in the thicker lamellar units had more cell-cell contacts of all types. A difference in stress-resisting properties of the inner two-thirds of the wall compared to the outer third is postulated in accordance with models in which the innermost lamellae support the high tension (77). Intercellular contacts were appositions, interdigitations, intermediate junctions, and nexus junctions. The latter were increased in hypertensive rats; possibly a decreased intercellular cohesion as a result of the shift from appositions and intermediate junctions (adhesion) to nexus junctions (communication) predisposes to degeneration of the media with ectasia, aneurysm or dissection formation in hypertension (78).

3.2.4 Cellular and neural effectors of the vessel wall

Monocytes, macrophages and vascular dendritic cells

Monocytes are constantly recruited and attracted to the endothelium through leukocyte chemoattractants secreted by EC, and these cells migrate into the intimal and subintimal layer after dissolving the basement membrane and internal elastic lamina. Some of the monocytes transform into macrophages and remain in the intima and media where they dispose of the occasional cellular debris and can become destructive in atherosclerosis (79). The other monocytes undergo transformation into dendritic cells after re-exiting the endothelium, and then migrate to local lymph nodes where they can activate clonal T-lymphocytes (80). This process has drawn attention to the fact that the vessel wall plays an important role in local and systemic immune regulatory mechanisms, and is at the origin of the term VALT or vascular-associated lymphoid tissue. This shows one of the possible ways in which systemic reactions to vascular diseases and vice versa might be mediated (81,82).

Vascular innervation

Subadventitial SMC are in direct contact with sympathic vascular nerve fibers. SMC contraction and dilation are regulated through adrenergic input, while parasympathic cholinergic neurons cause vasodilation (SMC relaxation). A mutual feedback mechanism exists between SMC and nerve fibers. Adventitial and subadventitial SMC secrete nerve-growth-factor, and it has been shown in cerebral muscular arteries that sympathic denervation causes significant SMC hypertrophy with an increase of medial and adventitial collagen (83). The hypertrophied SMC show ultrastructural modifications consistent with a shift to the synthetic, metabolic phenotype. Apparently, the suppression of a regulatory trophic factor linked to the presence of sympathic nerve fibers causes this shift. The sympathic nervous system appears to have a key role on the long-term

regulation of vascular structure (84), so that sympathomimetic drugs may well have far-reaching effects on the vascular wall stability.

3.2.5 Vasa vasorum

Oxygen and nutrients diffuse to the SMC from the vessel lumen and from the vasa vasorum. Most normal arteries have an extensive network of vasa in the adventitia. When the thickness of arteries exceeds the diffusion capacity of nutrients from the lumen (larger muscular or atherosclerotic arteries), vasa vasorum extend into the media and intima. They respond to vasoactive stimuli and can regress in response to regression of atherosclerotic lesions. Blood flow to the arterial wall can be increased through enlargement of pre-existing vasa or through neovascularization; and reduced by active constriction or through involution of existing vasa.

The pathophysiologic significance of vasa vasorum in normal and diseased arteries is related to their structure: vasa in the intima-media are thin-walled endothelial cell tubes with thin or absent medial smooth muscle cells. They are therefore prone to collapse and rupture (microtears) in response to arterial pressure, mechanical forces within the artery, (see mechanical forces 3.3.2, vasomotion 3.3.3) necrotic substances from vascular lesions and vasospasm. Vasa also provide the artery with a vast absorptive endothelial surface that has important implications for arterial lipid kinetics as well as delivery and removal of neurohumoral agents from the vessel wall. These properties have lead to speculation about their role in the pathogenesis of atherosclerosis, plaque rupture and thrombosis, medial ischemia as a cause for arterial dissection (CMN, MMD) and aneurysm, post-angioplasty restenosis and post-stenotic dilation (85).

3.3 Mechanical forces acting on the vessel wall

Various mechanical forces affecting the vessel wall also influence the profile and behavior of endothelial and smooth muscle cells. Cyclic mechanical strain in particular as experienced by the SMC during the pulse wave has the ability to profoundly affect cell growth, phenotype and synthetic response via intracellular signaling pathways (86).

3.3.1 Biomechanics, fluid mechanics and the carotid bifurcation

The singular flow patterns in the carotid bifurcation play an important part in shaping the vessel wall and intimal profile. A branch of physics is concerned with the behavior of fluids and has observed flow patterns in biological systems, in particular those in the carotid bifurcation.

Computational fluid dynamics

The advent of technologies such as angiography, duplex color-coded ultrasound and MRI angiography has provided us with means of studying arterial blood flow in humans in vivo. These measurements, particularly those obtained from magnetic resonance imaging, have led to the development of a field of mathematics known as CFD (Computational Fluid Dynamics). With the help of complex mathematical and biophysical models it has become possible not only to visualize the blood flow in carotid models based on MRI data (87,88) but also to perform in vivo measurements of blood flow, flow rates and velocity and shear stress variation along the vessel wall. The carotid bifurcation is a model particularly suited to the observation of the influences of wall shear stress, because of its special geometry with different secretory profiles, opposing a high-velocity flow region with high shear stress on the divider side to a low-velocity, turbulent, oscillating-shear zone on the external side, in the carotid bulb (89,71).

Vascular wall adaptation

As these models become more sophisticated, they allow a fascinating glimpse of the processes which shape and influence vascular geometry. Operations on the carotid bifurcation are routinely performed for obstructive carotid disease, and the ability to better diagnose and classify the extent of stenosis and flow alteration has an impact on the operating indications. Vein and prosthetic grafts as well as carotid endarterectomy alter the carotid bifurcation and its flow properties (90). Modeling the behavior of fluids under different circumstances and assessing the regions of highest and lowest shear has created a map of turbulence zones showing remarkable concordance with sites of early atherosclerotic lesions (89). Measurements performed in these models and verified by in vivo observations show that in order to maintain wall shear stress in a range of values around 15 dyne/cm^2 (endothelial quiescence and atheroprotection) (91, 92), arteries adapt their diameters and profile through constriction and myointimal hyperplasia in zones of lower shear stress. The intimal thickening reduces the size of low shear regions and the new geometry yields more even stress distribution along the bifurcation (93). Low shear (<4 dyne/cm^2) stimulates an atherogenic phenotype and triggers proliferation of intimal SMC.

3.3.2 Mechanical forces and vessel wall morphology

Three principal fluid-induced mechanical forces act directly upon the vascular wall. **Pressure** is created by hydrostatic forces and its vector is perpendicular to the vessel wall; **circumferential stretch** primarily affects medial SMC and is occasioned by the pulse wave, its vector is longitudinal and tangential to the direction of blood flow; and lastly, **shear stress** is the result of the moving blood, affects endothelial cells most, and its vector is parallel to the blood flow.

SMC are oriented in a helicoidal arrangement at an angle of about 20° – 40° to the longitudinal axis of the vessel, corresponding to a 50° – 70° angle between

the long SMC axis and the resulting vector of the distending forces. This SMC alignment is responsive to changes in the magnitude of strain, is reversible and plays an important part in determining the viscoelastic properties of the blood vessel. In response to heightened blood pressure, the vascular media expands due to SMC hypertrophy and/or hyperplasia. Tests done on the elastic properties of aortic tissue in different directions showed interesting results: samples of aortic arch stretched in the radial direction failed at significantly lower tension values (61.4 +/- 4.3 kPa) than samples exposed to circumferential and longitudinal stretch (151.1 +/- 8.6 kPa and 112.7 +/- 9.2 kPa, respectively). Microscopically, the radially stressed samples revealed SMC torn loose from their attachments to each other and to adjacent elastin. The aorta is usually subjected to radial compressive stress, and its resistance to radial stretch is much lower than to circumferential or longitudinal stretch, which also occur during the pulse wave. The results could explain why dissections propagate so readily once the initial tear has occurred (94).

Mechanical stress and SMC response

As already seen during vasculogenesis, mechanical strain/stretch is a powerful and independent activator of SMC growth, matrix secretion and proliferation. This effect is mediated in part via platelet-derived growth factor (PDGF) and AT II, yet there is evidence that mechanical stretch also has a direct influence on SMC, and that the response to stretch differs in cultured cells (proliferation) and organ cultures (hypertrophy). This difference in response is probably due to the presence or absence of a coherent matrix surrounding the SMC. Despite an increased matrix secretion, stretched SMC within an organ culture retained a well-differentiated contractile phenotype, confirming the supposition that structured matrix influences the SMC phenotype. Only excessive stretch altered the SMC secretory profile, under physiological strain SMC were quiescent and contractile (53,73).

Integrins and mechanotransduction

The effectors of mechanical stretch on SMC physiology are believed to be integrins (54), a class of transmembrane glykoproteins attaching the cell to the surrounding matrix proteins and linked to the cytoskeleton via the focal adhesion complex (65). Mechanical stress activates MAP-kinase in SMC and is involved in strain-induced proliferation dependent on the local matrix environment. The proliferative response in differentiated SMC is unlike that found in dedifferentiated, embryonal-type synthetic SMC. This appears to argue for at least two different activation pathways for SMC in the vascular wall, probably strongly influenced by specific and various matrix-integrin interactions.

Ion channels

Stretch-activated ion channels and changes in membrane potential may also play a role in mechanotransduction. Mechanosensitive channels have been detected in numerous cell types and seem to play an important role in orchestrating the EC response to shear stress. There is also strong evidence that SMC can alter their sodium and potassium ion conductivity in response to stretch and that membrane depolarization and modulation of vascular tone can be observed (95).

3.3.3 Vasomotion

Vasomotion is the term applied to oscillating, synchronized, chaotic vascular micro-contractions found in arterial blood vessels, primarily in the microcirculation but also in major elastic arteries. It shows two distinct frequency domains and seems to change in response to central nervous and local inputs, allowing a more effective tissue oxygenation in low-oxygen regions and playing a role in the recirculation of lymphatic and tissue fluid. Vasomotion is originated in specialized pacemaker cells at vascular junctions and shows a pulse-wave spreading pattern in the near vicinity (95). The vasomotion pattern altogether is pulse-independent and shows synchronized frequency oscillations throughout

the body. Vasomotion conduction in SMC may be impaired through phenotypic SMC alteration, sympathomimetics and neurohumoral factors affecting the SMC. Membrane hyperpolarization, depolarization, desynchronization and loss of contractile ability in SMC seem to be the responsible factors (96,97,98). Impaired vasomotion as reflected in irregular and de-synchronized SMC contractions might negatively affect tissue oxygenation and increase intercellular stretch, predisposing to dissection in weakened wall areas.

3.4 Brief review

Vessel wall cells have a common mesenchymal origin except for some SMC in elastic arteries that derive from the embryonic neural crest. The main difference lies in secretory activity, neural crest-derived cells producing a predominantly elastic matrix.

The endothelium is a sensitive receptor and effector organ for various neurohumoral, mechanical, metabolic and inflammatory signals. The effect of endothelial cells on surrounding tissue and cells is mediated through the expression and release of various cytokines, growth factors and cell adhesion molecules. These signaling molecules also affect the morphology and behavior of the EC and may support a quiescent, growth-inhibiting and antithrombotic profile or trigger the change into an activated, pro-thrombotic and pro-proliferative profile. In the intima and subintimal media, local macrophages and locally imprinted dendritic cells derived from circulating monocytes form the vascular-associated lymphoid tissue and play an important role in local and systemic immune response The VALT serves both as a monitoring and effector organ, with dendritic cells as an important afferent limb of the cellular immune system.

The vascular system is complex, with functions in the active modulation of metabolic and hemodynamic processes as well as in transport. Vascular smooth muscle is the primary effector component of the vessel wall and is regulated in its activity by local endothelial cell and neural activity in addition to circulating substances. Vascular smooth muscle cells are embedded in a matrix composed of various proteins and exist in an elongated, aligned, contractile, quiescent and well-differentiated state in the most part of the middle and exterior media. Following signals from the endothelium or through mechanical stress, SMC can alter their appearance and secretory profile. Activated cells, usually in the vicinity of the lumen or the vasa vasorum, show a particular behavior: when the activated SMC are not firmly anchored by matrix proteins with a growth-inhibitory effect as happens during vascular lesions, they will dedifferentiate and reexpress embryonal autonomous growth factors, which enable them to proliferate and migrate to the site of injury. Activated secretory SMC within a growth-restraining matrix change their intercellular contacts and shift to a matrix-secreting profile. The ordered alignment is lost, and loosely bunched SMC can be found, usually in the subintimal layer of the media. Dedifferentiated SMC in loose arrangements are mostly present in the subintimal layer of the media.

Matrix proteins are ubiquitous in the vessel wall, and serve as anchorage for SMC and cytoskeletal proteins and as a template for orderly SMC arrangement. Mechanical forces acting on the vessel wall are principally borne by the matrix proteins, which in turn adjust SMC tension and reactivity. Some matrix proteins are inherently growth-inhibitory and promote a contractile, differentiated SMC phenotype in their vicinity; others have a proliferation- and migration-enhancing effect. During angiogenesis and vascular repair, matrix is destroyed by selective proteases secreted by EC, SMC and macrophages so that local EC and SMC can dedifferentiate and regain mobility. Elastases, collagenases, proteases and matrix metalloproteinases are prominent among the matrix-degrading enzymes.

Subadventitial SMC are in direct contact with sympathic vascular nerve fibers and are instrumental in adjusting vasomotor tone to the central nervous inputs. SMC and nerve fibers mutually influence each other via the secretion of NGF (SMC) and controlling trophic factors (NF), creating a feedback loop between SMC and neural fibers.

Vasomotion is the term applied to oscillating, synchronized, chaotic vascular micro-contractions found in arterial blood vessels. It originates in specialized pacemaker cells at vascular junctions, is pulse-independent and shows synchronized frequency oscillations throughout the body. Vasomotion conduction in SMC may be impaired through SMC phenotypic alteration, sympathomimetics and neurohumoral factors affecting the SMC.

4. Material and Methods

The corpses presented for autopsy in the forensic department either receive a full forensic autopsy if commissioned by the state prosecutor, or a routine autopsy in cases that are scheduled for cremation if the coroner specified “unknown or unnatural cause of death”. Every year, between 600 and 1000 autopsies are performed in the university forensic medical department. During the storage and examination period, the bodies are in the legal custody of the Department of Forensic Medicine.

4.1 Inclusion criteria

Tissue samples were obtained from bodies scheduled for forensic or routine autopsy. We sampled corpses of people aged 18 to 65 years without signs of decay other than localized green discoloration in the right lower abdominal quadrant due to bacterial translocation from the coecum. This first sign of decay can be observed early after death while the remaining organs remain nearly intact. The lapse of time between death and autopsy had to be less than eight days (in cold storage at +4°C). We inspected each body for signs of connective tissue disease (habitus, history). During the cervical preparation, the left carotid bifurcation was incised lengthwise and the state of the vessels assessed. Cases in which vessels showed macroscopically visible atheromatous or arteriosclerotic lesions greater than isolated fatty streaks were excluded. If the left bifurcation and descending aorta seemed intact, we removed the right carotid bifurcation in toto and a portion of the aortic arch. Fifty-four cases were included; the details are given in table 1.

Table 1: Sample demographics and cause of death

N.	Age	Sex	BMI	Circumstances	Cause of death
1	19.0	F	22.03	IVDU	Overdose, respiratory failure
2	55.0	M	17.99	Liver cirrhosis (C_2H_5OH)	Gastrointestinal hemorrhage
3	27.0	M	27.17	IVDU	Overdose, respiratory failure
4	32.0	M	23.39	Motor vehicle accident	Asphyxiation (thoracic compression)
5	44.0	F	29.40	Hypertension	Left ventricular failure
6	57.0	F	16.80	Liver cirrhosis (C_2H_5OH)	Gastrointestinal hemorrhage
7	57.0	F	23.83	Suicide by defenestration	Massive cerebral and thoracic trauma
8	20.0	F	19.69	Motor vehicle accident	Open skull fracture, ruptured aorta
9	47.0	M	28.96	Found in apartment	Pneumonia
10	47.0	F	18.39	None given	Myocardial infarction
11	52.0	M	28.72	Extramarital activity + Viagra	Cardiac arrest
12	53.0	F	29.41	Depression and suicide	Prescription drug overdose, resp. failure
13	46.0	M	22.30	Liver cirrhosis (C_2H_5OH)	Gastrointestinal hemorrhage
14	61.0	M	26.18	Acute headache and death	Subarachnoid hemorrhage
15	55.0	M	22.95	Suicide	Cyanide poisoning
16	43.0	F	17.30	Old oven	Carbon monoxide poisoning
17	47.0	M	24.07	None given	Pericardial tamponade
18	39.0	M	24.22	Debts, suicide by train	Massive trauma, dismemberment
19	27.0	M	24.65	IVDU	Overdose, respiratory failure
20	25.0	M	22.26	IVDU	Overdose, respiratory failure
21	42.0	F	20.50	IVDU	Cerebral hemorrhage
22	39.0	M	22.03	Suicide by defenestration	Massive cerebral and thoracic trauma
23	63.0	F	20.23	Psychosis, defenestration	Massive cerebral and thoracic trauma
24	19.0	F	21.34	Honor killing	Penetrating stab wound to heart
25	26.0	F	19.03	Murder? Suicide?	Hanging, hypoxia
26	60.0	M	18.73	Motor vehicle accident	Open skull fracture
27	47.0	F	21.04	Domestic violence	Slit throat, cerebral hypoxia
28	24.0	F	17.28	Cocaine, suicide by train	Massive thoracic trauma
29	18.0	M	20.10	MVA, 3 days in ICU	Multiple organ failure, polytrauma
30	26.0	M	28.43	Motor vehicle accident	Aortic rupture, deceleration trauma
31	26.0	F	15.99	Bulimia	Hyperglycemia, metabolic acidosis
32	55.0	M	24.18	Suicide	Hanging, hypoxia
33	44.0	M	30.03	Suicide	Cyanide poisoning
34	26.0	M	24.41	Allergy to nuts, airline food	Anaphylactic shock
35	51.0	M	25.37	Diabetes mellitus	Hyperglycemic coma
36	64.0	M	28.43	Suicide	Hanging, hypoxia
37	22.0	F	17.30	IVDU, hepatitis C	Overdose, asphyxiation
38	54.0	M	18.52	Bronchial carcinoma	Pulmonary hemorrhage, asphyxiation
39	36.0	M	23.53	Motor vehicle accident	Thoracic compression, asphyxiation
40	60.0	F	28.71	Motor vehicle accident	Massive open skull fracture
41	26.0	F	18.92	Accidental defenestration	Massive cerebral and thoracic trauma

N.	Age	Sex	BMI	Circumstances	Cause of death
42	27.0	M	19.68	Suicide	Hanging, hypoxia
43	54.0	M	37.39	Cardiomegaly, Obesity	Global heart failure
44	18.0	F	29.08	Motor vehicle accident	Polytrauma
45	40.0	F	22.44	IDDM, diabetic neuropathy	Cardiac failure
46	19.0	M	23.03	MVA, Hit-and-run	Open skull fracture, hypoxia
47	29.0	M	18.34	Diabetes mellitus	Hyperglycemic coma
48	59.0	F	18.97	Liver cirrhosis (C_2H_5OH)	Right ventricular failure
49	45.0	F	26.60	Suicide	Hanging, hypoxia
50	21.0	F	20.92	Coagulation disorder?	Pulmonary embolism
51	59.0	M	25.91	Liver cirrhosis + smoker	Cardiac failure
52	28.0	M	24.10	Suicide (firearm)	Partial decerebration
53	28.0	M	23.20	IVDU	Cardiac failure
54	24.0	M	23.00	IVDU	Overdose, asphyxiation

IVDU = intravenous drug use, MVA = motor vehicle accident, IDDM = insulin-dependent diabetes mellitus

4.2 Sample processing

The samples were fixed in 4.5% buffered formalin for at least 48 hours. Then the surrounding fatty tissue was removed and thin cross-sections were cut from the common, internal and external carotid close to the carotid bulb. These slices and the aortic sample were embedded in paraffin and serially cut into 5-6 µm cross-sections on a Microm HM 350 microtome (Microm, Heidelberg, Germany).

The obtained serial slides of each sample were stained using hematoxylin and eosine, alcian blue and elastica-van Gieson for light microscopy in order to evaluate cell nuclei, SMC and matrix fibers and elastic tissue. Immunocytochemic staining (APAAP/ Fast Red) was performed for collagen IV to depict the basement membranes and stromal architecture. Collagen IV was chosen since it is present throughout the basement membranes and reflects the cellular damage and cystic lesions found in cases of aortic dissection (99).

The slides were examined using an Olympus binocular microscope with 40x-600x magnification. Photographs were taken on an Nikon Optiphot II microscope with adapted camera using Agfa 200 ISO color slide film.

4.3 Examination and evaluation

The samples were first screened for recurrent variations in the vascular wall in order to establish a control pattern for the carotid bifurcation (boundary zone between elastic and muscular artery); and then each slide was examined in detail and evaluated for histological changes associated with spontaneous cervical artery dissection.

Cystic medionecrosis, mucoid degeneration, fibromuscular dysplasia, focal elastinolysis, dissection, kinking and/or coiling as well as inflammatory infiltration of the vessel wall were search parameters. Each cross-section was divided radially into thirds and each vessel wall layer was examined, the medial layer being divided into three concentric layers. The presence of alterations in the cross-section was rated grade I-III depending on the number of radial thirds affected.

5. Results

5.1 Demographic data

Seven out of fifty-four (12.9%) examined cases showed lesions resembling cystic medionecrosis (CMN), fibromuscular dysplasia (FMD), mucoid media degeneration (MMD), elastin defects (ELD), dissection or intramural bleeding (DBL), and localized inflammation (INFL). All positive samples came from male corpses. The remaining 47 samples were used as controls and displayed only minor alterations of architecture associated with SMC metabolism or aging.

The mean age in cases 1-7 was 39.9 years (range 19-64) versus 39.2 years for all (range 18-64) and 40.5 years for all males (range 18-64). Mean BMI in cases 1-7 was 25.9 versus 23.5 for all and 24.2 for all males. The M: F ratio in the sample group was 1.34 (31:23). Eight of the subjects in the sample group (14.8%) were intravenous drug users (M: F = 1.6); case 1 was the only one of these showing distinctive alterations in SMC and vascular architecture. In cases 1, 2, 4 and 5, death was due to accident or suicide, in case 3 death was due to cardiac arrest and autopsy revealed excessive heart weight (>550 g), which correlated with massive overweight (BMI 28.7). In case 6 right ventricular failure associated with liver cirrhosis was the most likely cause of death, while in case 7 ingestion of nuts lead to fatal anaphylactic shock.

Since the selection of cases was neither randomized nor reflective of the general population, statements about frequency of lesions cannot be made. The lesions will be illustrated for each case.

5.2 Morphological findings

Three cases showed dissection and/or intramural bleeding (DBL); the extent of the lesions varied from complete medial dissection of the ICA with intussusception in case 4 (Fig. 4a-c) to coexisting old and recent medial tears in ICA and ECA in case 3 (Fig. 3a-d) to a minute subadventitial dissection of the ECA in case 2 (not shown).

Mucoid degeneration of the media (MMD) occurred twice, in case 4 it was present in most of the intussuscepted media (Fig. 4a,b), in case 6 it was present only in the subintimal aortic media (Fig. 6a,b).

Cystic medionecrosis (CMN) appeared in cases 2 (Fig. 2a,b) and 7 (Fig. 7a,b) and was present both in the aorta and in the common carotid artery. Patterns resembling fibromuscular dysplasia (FMD) were present in cases 1 and 5 (Fig. 1a,b, 5a-c) and were found predominantly in the internal carotid artery. Elastin defects (ELD) in all cases included doubling and fragmentation of and/or gaps and holes in the internal elastic lamina (IEL) (Fig. 5c-e), elastic fiber defects in the media such as local disruption or thinning and irregular patterning, and heightened but irregular accumulation around nodular SMC (Fig. 1b, 2a, 6b, 7b).

Inflammatory infiltrates (INFL) consisting of lymphocytes surrounding the vasa vasorum in the adventitia (as seen in the hematoxylin and eosin stain) were present but not pronounced in cases 1-5 and 7.

Cases 1-7 are shown with relevant sites. In order to place them in a context, normal and aged vessel walls are shown and the relevant age-dependant changes pointed out.

Table 2: Histological findings in cases 1-7

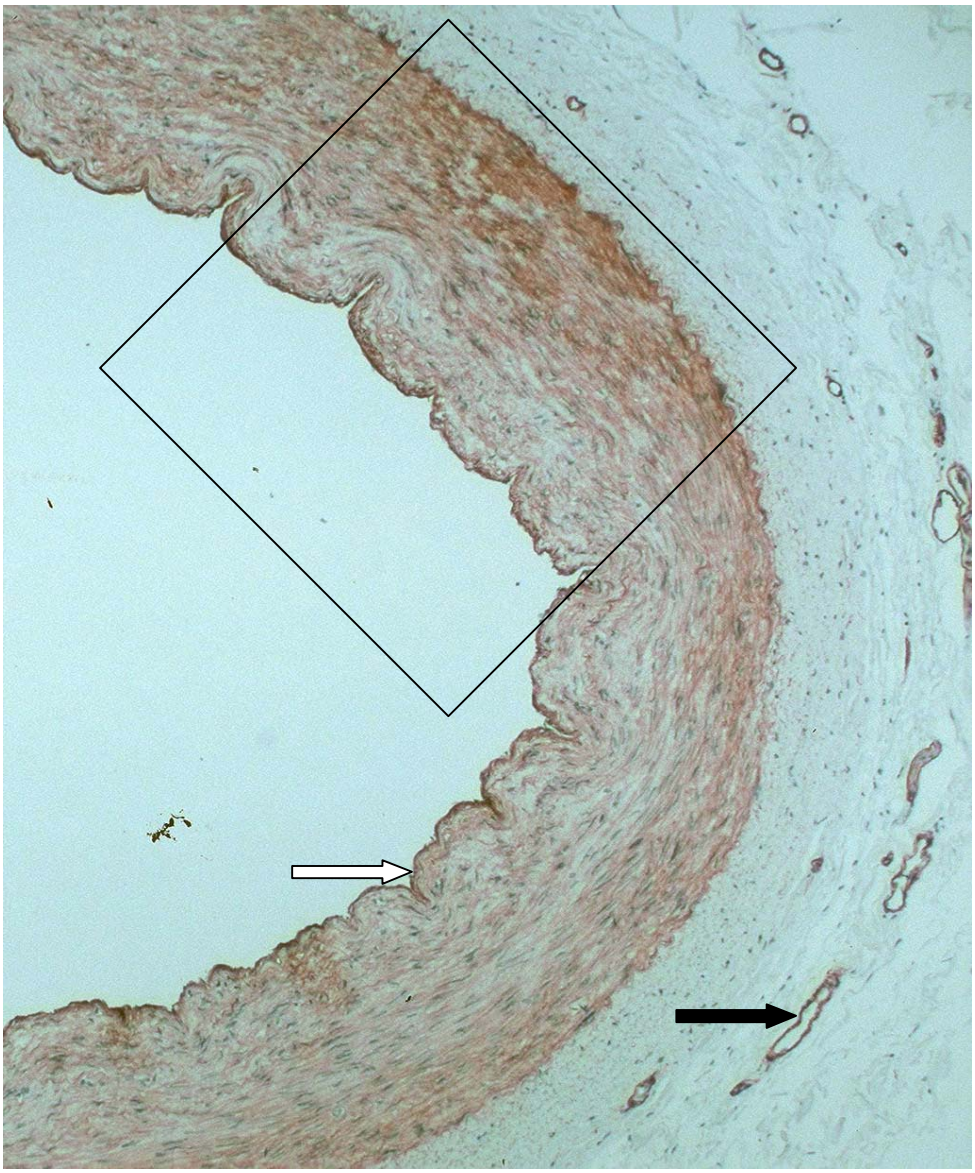
N.	Age	Sex	BMI	COD disease	arteries affected	DBL	MMD	CMN	FMD	ELD	INFL
1	27	M	27.2	IVDU							
				Hep C	ACC						
					ACI				+	+	
					ACE				+	+	+
					AOR						+
2	32	M	23.4	MVA							
					ACC			+			+
					ACI				+		+
					ACE	+					
					AOR			+		+	
3	52	M	28.7	CAR							
					ACC						+
					ACI	+			+	+	+
					ACE	+				+	+
4	64	M	28.4	HNG							
					ACC		+				+
					ACI	+	+		+	+	+
					ACE		+		+		
					AOR	+	+			+	+
5	19	M	23.0	MVA							
				IVDU	ACC				+	+	
					ACI				+	+	+
					ACE				+	+	
					AOR						+
6	59	M	25.9	CAR							
				LCI	AOR		+				
				NIC							
7	26	M	24.4	AS							
					ACC	+		+		+	+
					AOR	+		+		+	

COD = cause of death, IVDU = intravenous drug use (overdose), MVA = motor vehicle accident,
CAR = cardiac arrest, HNG = hanging, RVF = right ventricular failure, LCI = liver cirrhosis,
NIC = Nicotine abuse; AS = anaphylactic shock; CCA = common carotid artery,
ICA = internal carotid artery, ECA = external carotid artery, AOR = descending aortic arch

DBL = dissection and/or intramural bleeding, MMD = mucoid media degeneration,
CMN = cystic medionecrosis, FMD = fibromuscular dysplasia,
ELD = localized or general elastin defects, INF = inflammatory cellular accumulation around vasa vasorum

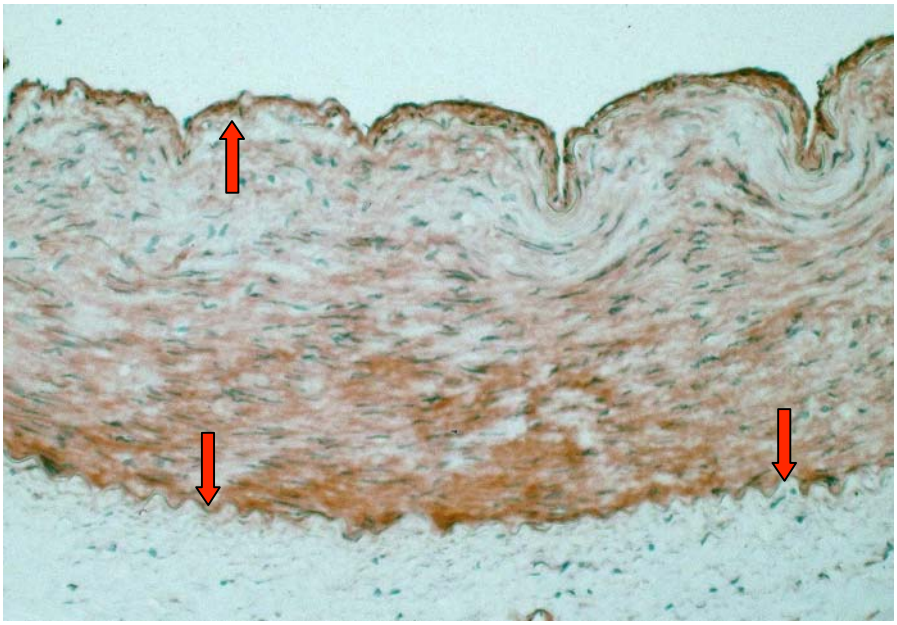
5.3 Figures

Internal carotid



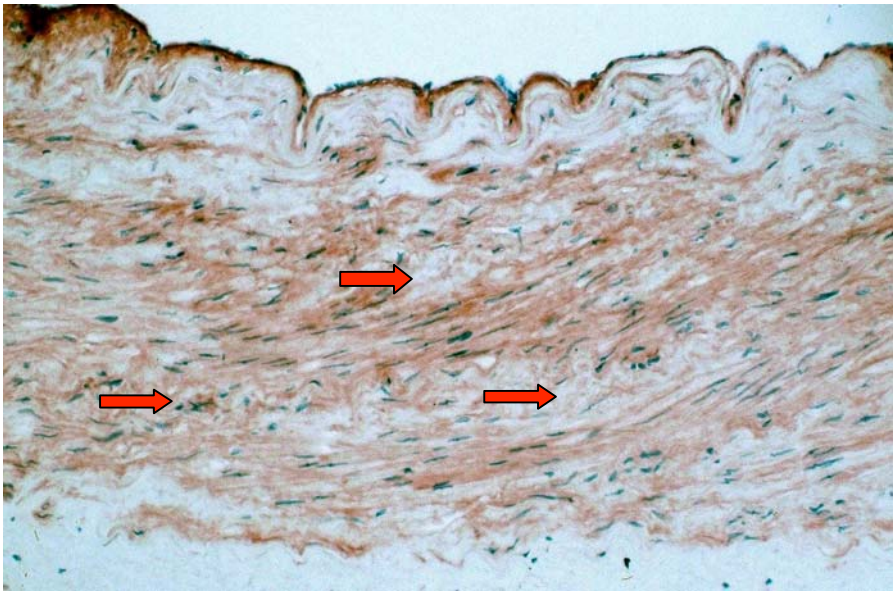
A1) Internal carotid artery, Collagen IV, 40x magnification

Internal carotid artery of a 26-year old woman. Intact media structures, external and internal elastic membrane, no intimal thickening. Normal, slightly irregular Collagen IV staining (red) in the intact media, as well as the EC basement membranes of the intima (white arrow) and vasa vasorum (black arrow). Inset below.



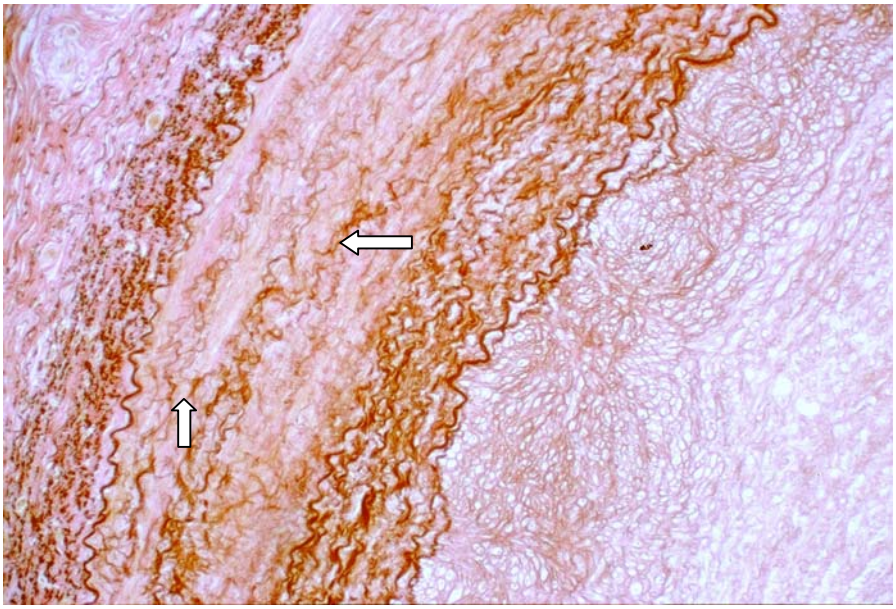
A2) Internal carotid artery, Collagen IV, detail, 100x magnification.

Elastic lamellae appear grayish-white and translucent (red arrows). This stain pattern is representative for most muscular arteries. The subadventitia is more structured than the subintimal media.



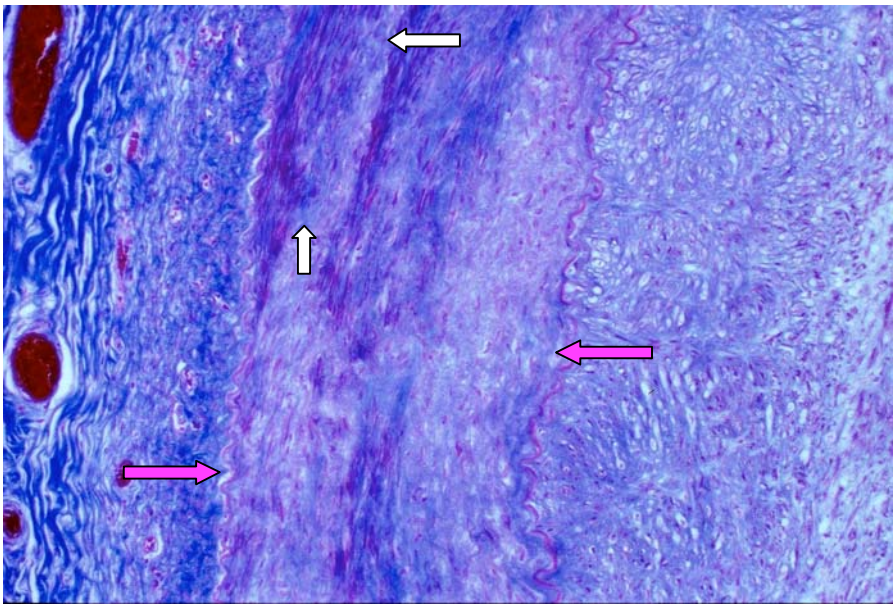
B1) Internal carotid artery, Collagen IV, 100x magnification.

Internal carotid of a 57-year old woman. This irregular stain pattern is typical for the transitional type arteries with elastic fiber bundles (red arrows) intercalated between the SMC bundles.



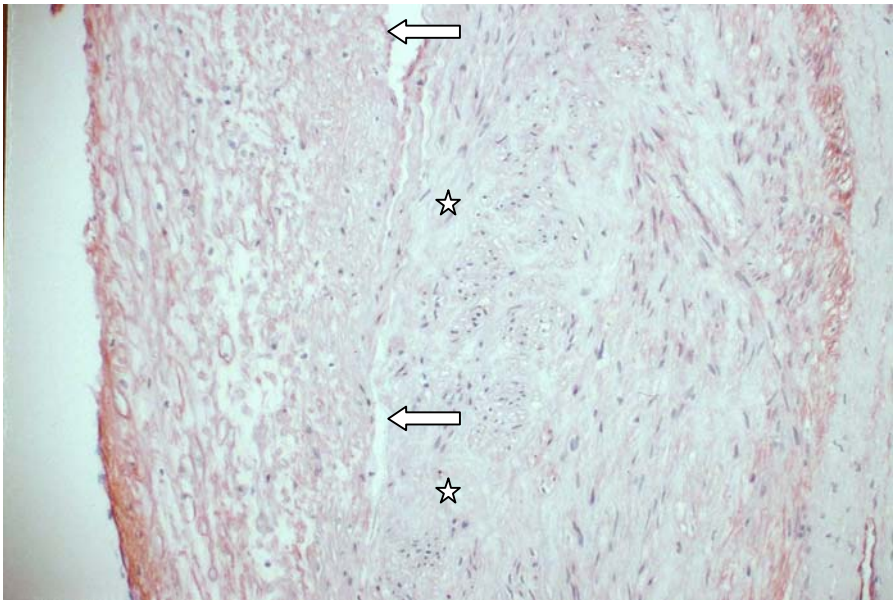
C1) Internal carotid artery, elastica- van Gieson, 100x magnification.

Transition pattern in the internal carotid of a 47-year old man. Note the interleaving of elastic lamellae and SMC areas. The thickened intima is visible right. The same wall section is shown in an azan stain below. Corresponding areas are pointed out in white arrows.



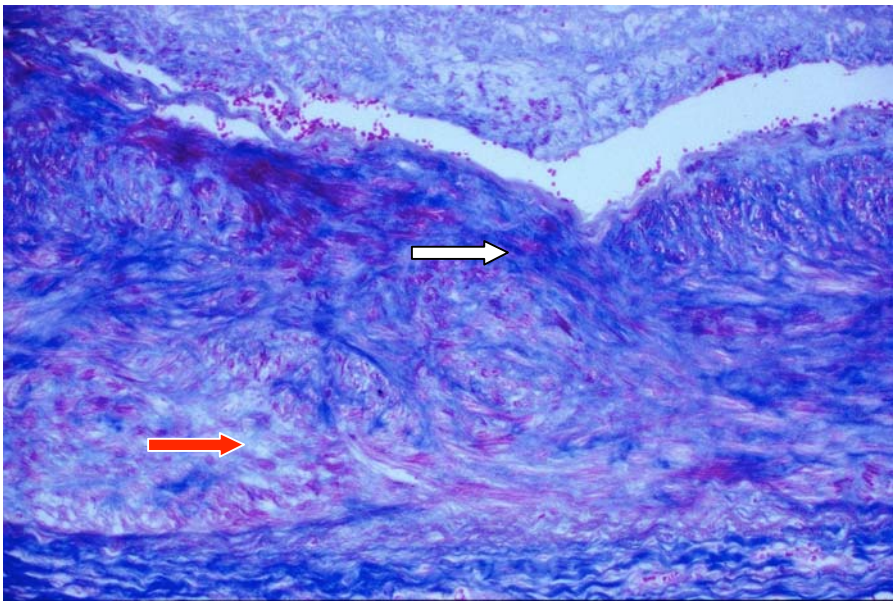
C2) Internal carotid artery, Azan blue, 100x magnification.

The media is delineated by the internal and external elastic lamellae (pink arrows). Engorged vasa vasorum can be seen left and top left (dark red).



D1) Internal carotid artery, Collagen IV, 100x magnification

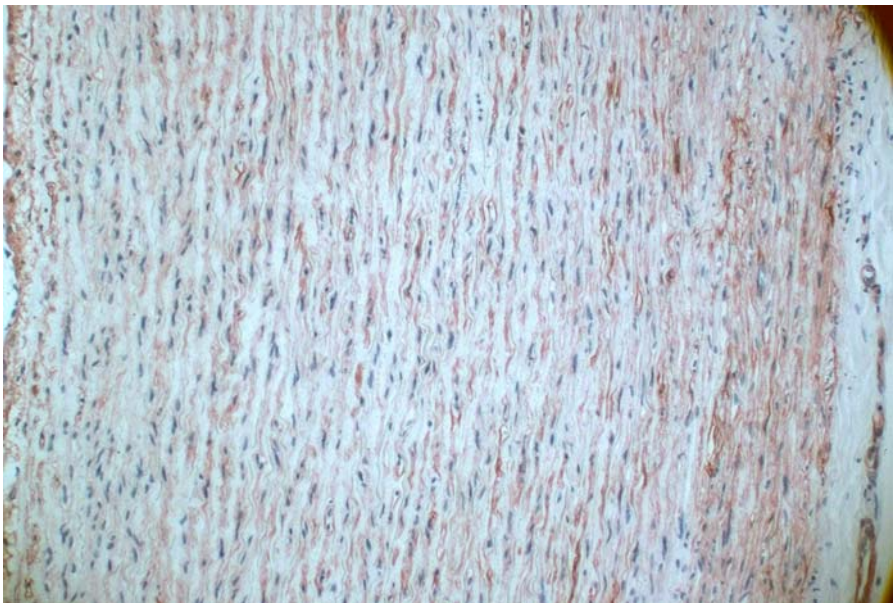
Internal carotid of a 60-year old man, showing intimal plaque (left) detaching from the medial wall (arrows). Poor Collagen IV staining in the media as a sign of SMC structure loss in the poorly oxygenated zone below the plaque (*).



D2) Internal carotid artery, Azan blue, 100x magnification

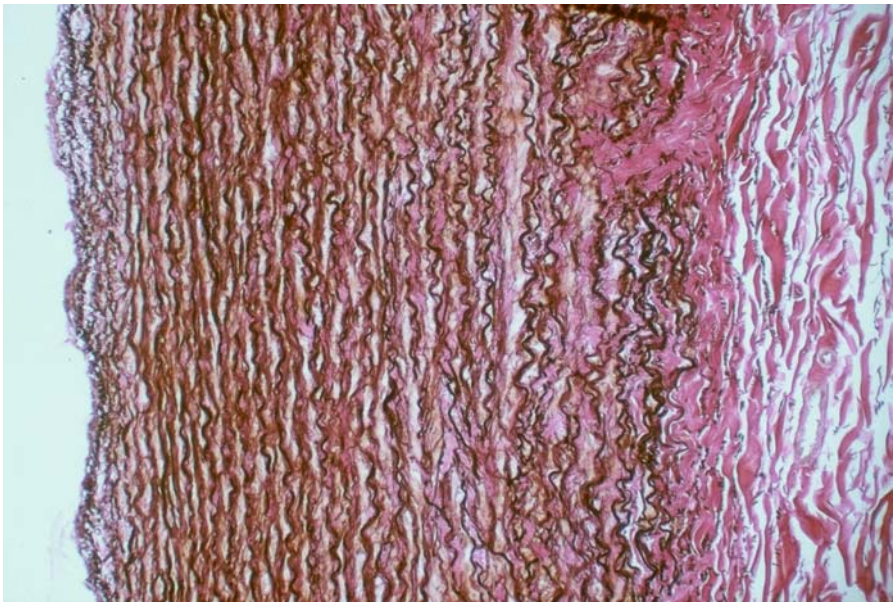
Same case. Whorls of SMC (purple) in media (red arrow) and bands of fibrous material with almost no SMC under plaque (white arrow). Plaque rupture may be a result of trauma during motor vehicle accident.

Aortic wall

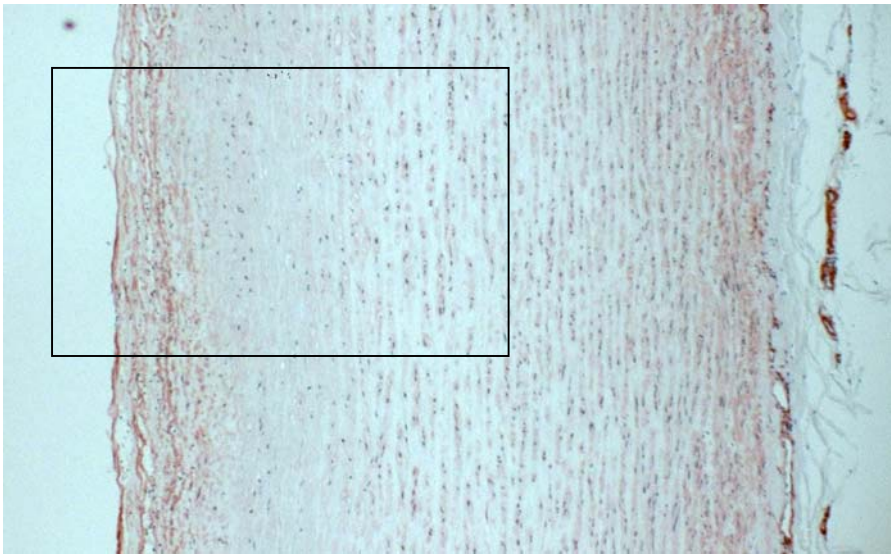


E1) Aorta, Collagen IV, 100x magnification.

Normal aortic wall pattern of a 19-year old woman. Regular Collagen IV layers (E1) (red) within the media alternate with regular layers of elastic lamellae (E2) (black). Compare with Collagen IV stain of older aorta below.

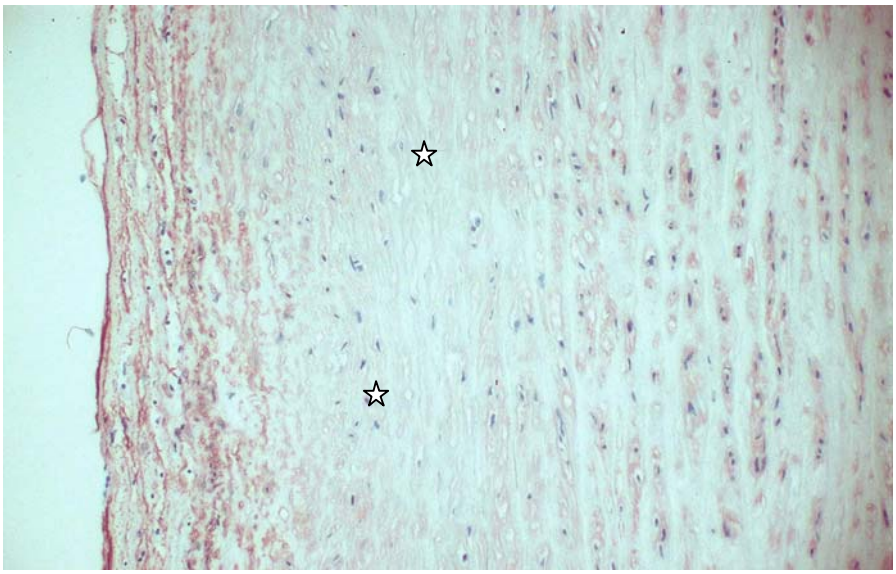


E2) Aorta, elastica- van Gieson, 100x magnification



F1) Aorta, Collagen IV, 40x magnification

Wall pattern of the aorta of a 63-year old woman. The basement membrane of vasa vasorum and fragmented layer pattern in the subadventitial and middle media retain patterned Collagen IV, while diffuse staining in the subintimal area (*detail) and bunched nuclei indicate disruption of orderly cell aggregation. Details (insert) below.



F2) Aorta, Collagen IV, 100x magnification

Case One (male, 27 y)

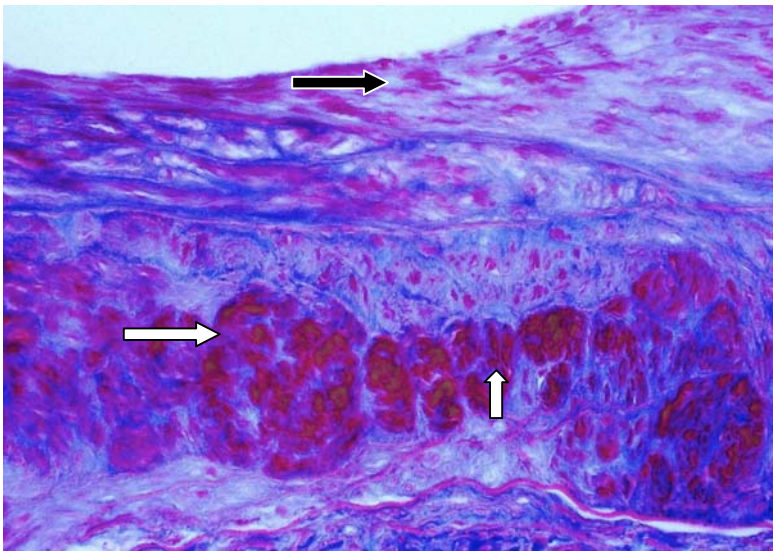


Fig. 1a) External carotid artery, longitudinal section, Azan blue, 200x magnification
SMC in nodular arrangement (white arrows) surrounded by ground substance (light blue) and collagen fibers (ultramarin blue), thickened intima with SMC proliferation (black arrow). Elastic fibers are pink (bottom). This pattern corresponds to that described for fibromuscular dysplasia.

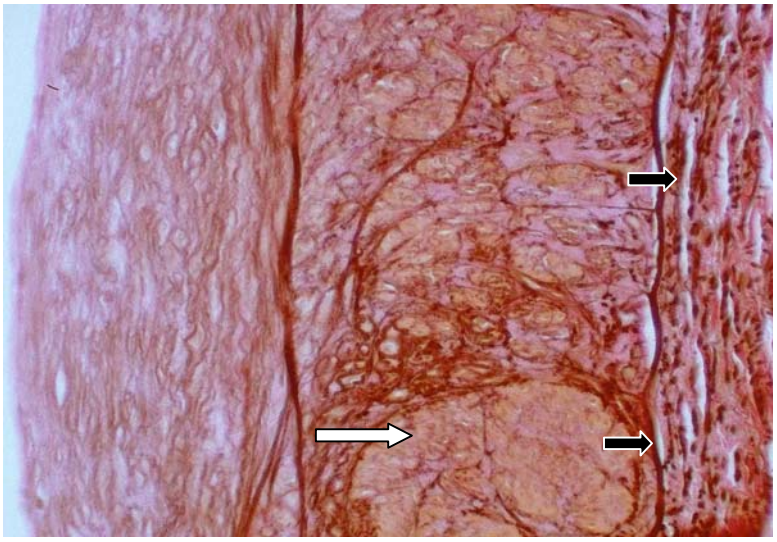


Fig. 1b) External carotid artery, longitudinal section, elastica- van Gieson, 200x magnification
SMC (orange) in nodular arrangement (white arrow) surrounded by elastic fibers (reddish-brown), thickened intima, and fibrosis of the adventitia (black arrow).

Case Two (male, 32 y)

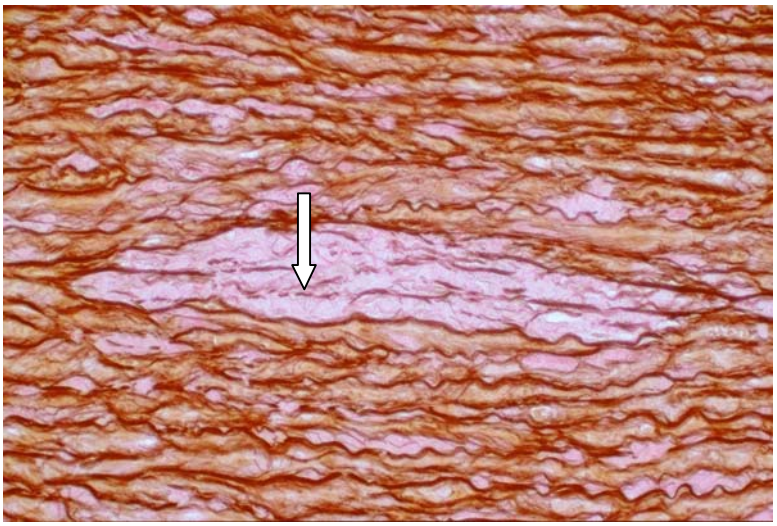


Fig. 2a) Aorta, elastica- van Gieson, 200x magnification

Aortic wall with cystic medial necrosis: absence of SMC, prominent ground substance and fragmentation of elastic fibers (white arrow).

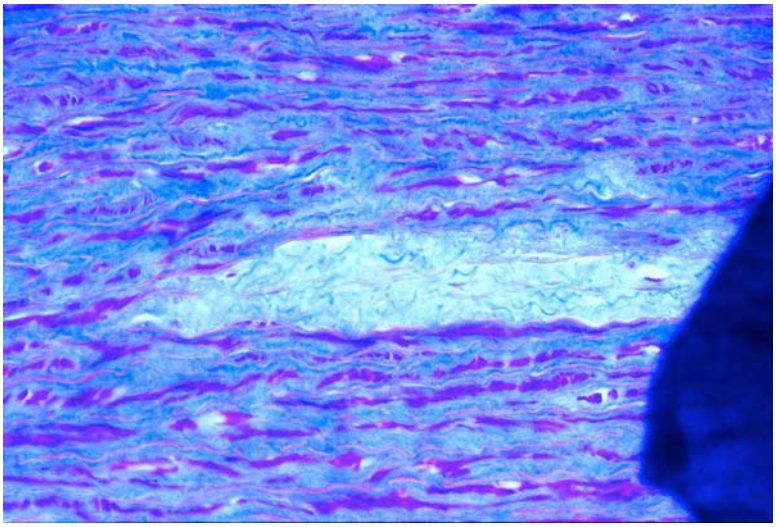


Fig. 2b) Aorta, Azan blue, 200x magnification

Aortic wall showing medionecrosis, absence of SMC (magenta), prominent mucoid ground substance (cyan) and disruption of elastic fibers (rose).

Case Three (male, 52 y)

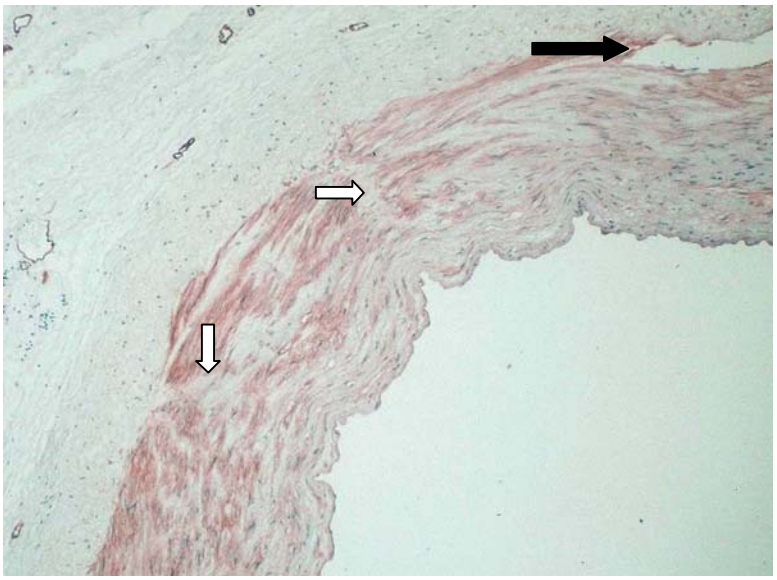


Fig. 3a) Internal carotid artery, Collagen IV, 40x magnification

Recent ICA dissection and medial scarring with irregularly arranged SMC. Enhanced collagen IV staining with appearance of partial scarring (white arrows) in the media. Subadventitial dissection seen top right (black arrow).

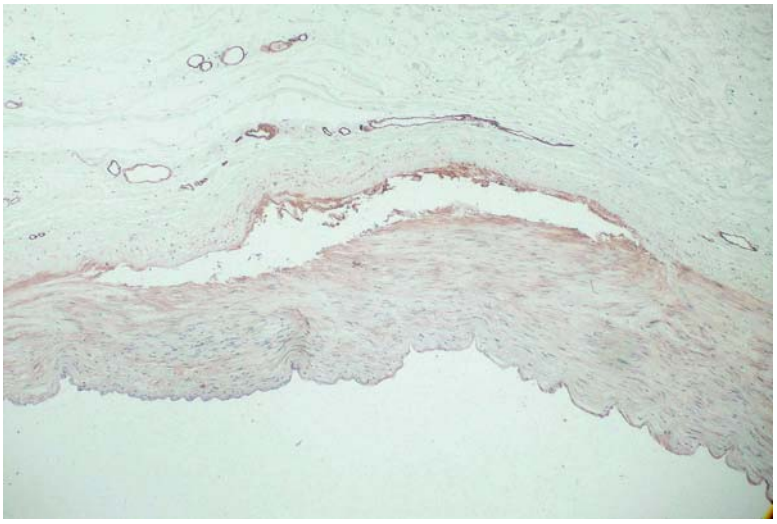


Fig. 3b) Internal carotid artery, Collagen IV, 40x magnification

ICA showing recent dissection in the subadventitial plane with dehiscence of media along the adventitial border.

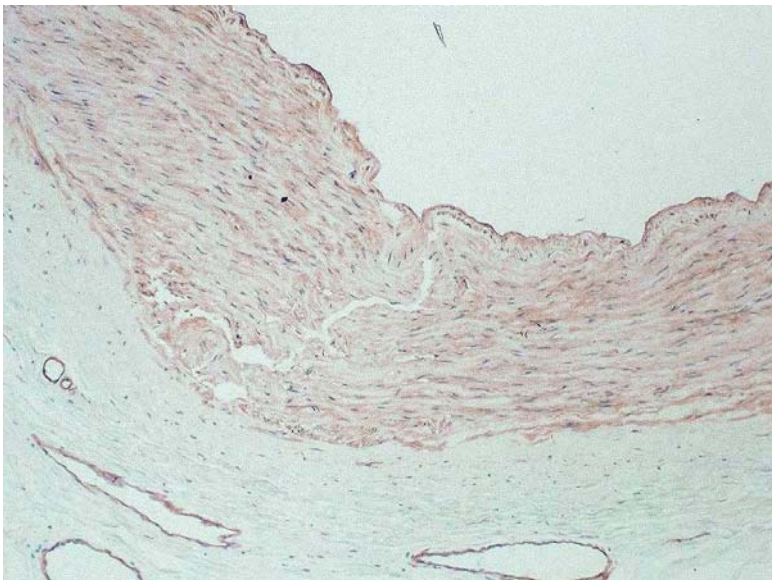


Fig. 3c) External carotid artery, Collagen IV, 40x magnification

Older radial tear in the external carotid with signs of SMC burgeoning, details below.

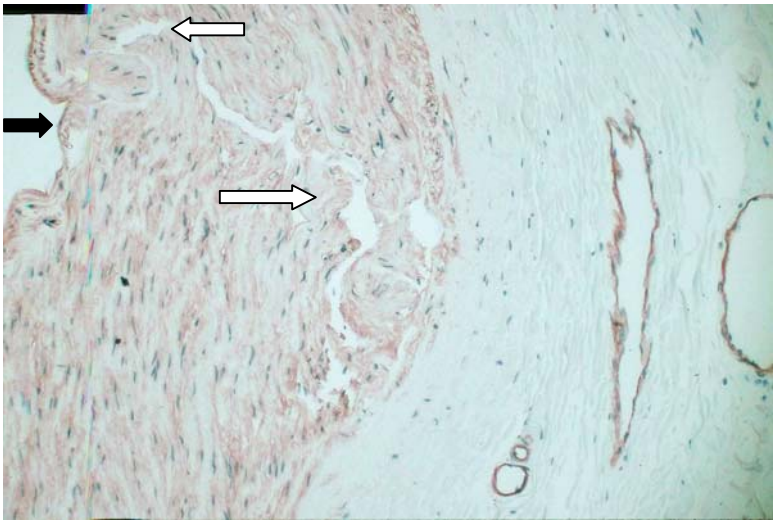


Fig. 3d) External carotid artery, Collagen IV, 100x magnification

(Detail from above) Older medial rupture (white arrows) with retracted intima (black arrow) and SMC organization along the tear walls. Adventitia right.

Case Four (male, 64 y)

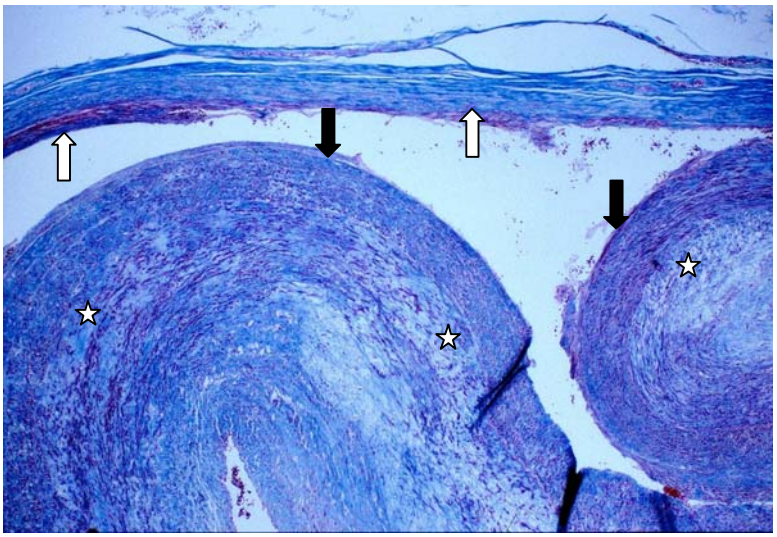


Fig. 4a) Internal carotid artery, Azan blue, 40x magnification

Internal carotid showing subadventitial dissection (white arrows) and intussusception (black arrows) with RBC in the false lumen, irregular SMC arrangement within the intussuscepted wall and mucoid degeneration with accumulation of ground substance in the intima-media (*).

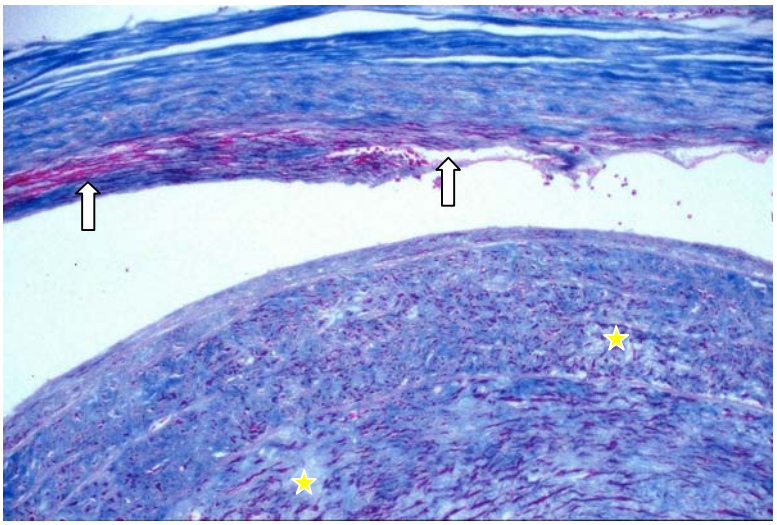


Fig. 4b) Internal carotid artery, Azan blue, 100x magnification

Detail of subadventitial dissection plane with intussusception of the intima-media (below). Intensely stained SMC along the adventitia-media (white arrows) and mucoid substance (stars) in the intussuscepted media.

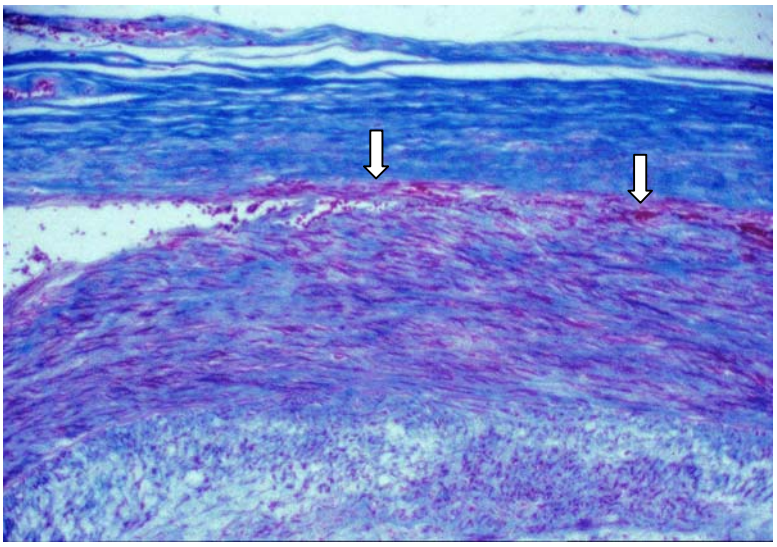


Fig. 4c) Internal carotid artery, Azan blue, 400x magnification

Detail (2) of the subadventitial dissection edge with intense SMC staining along the dissection plane (white arrows).

Case Five (male, 19 y)

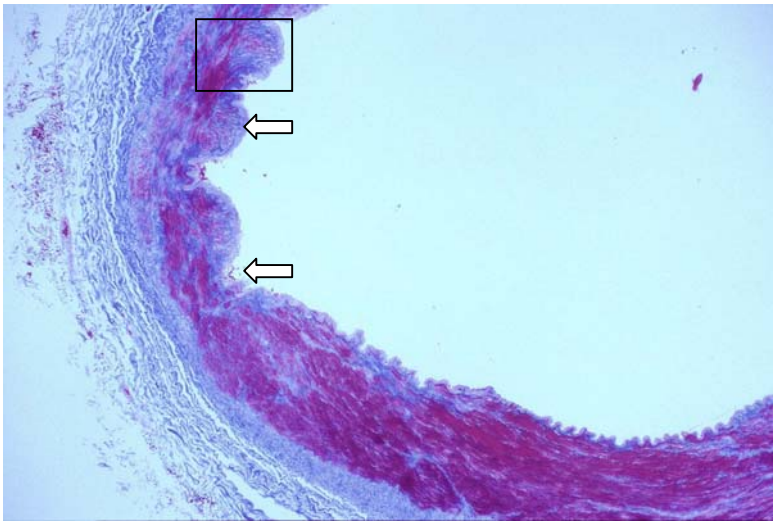


Fig. 5a) Internal carotid artery, Azan blue, 40x magnification

Internal carotid displaying alternating areas of thickening and thinning as described for FMD, as well as bunched SMC proliferation. Detail (box) below.

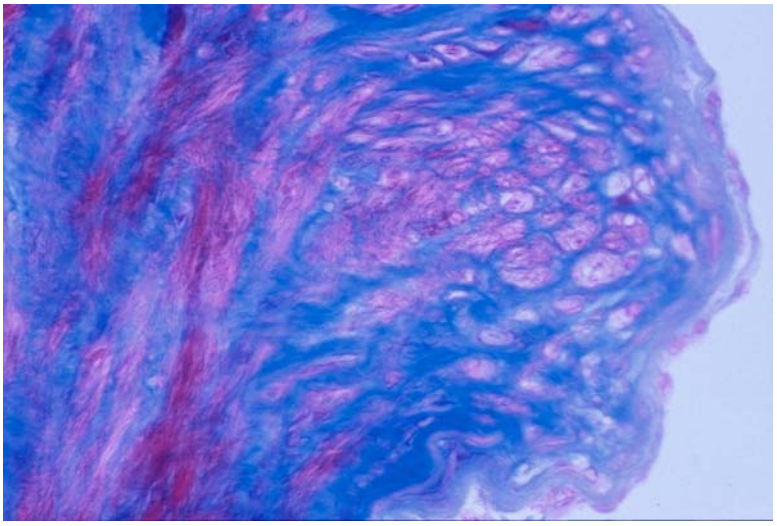


Fig. 5b) Internal carotid artery, Azan blue, 400x magnification

Detail with irregular SMC proliferation and nodular aggregation protruding into the lumen.

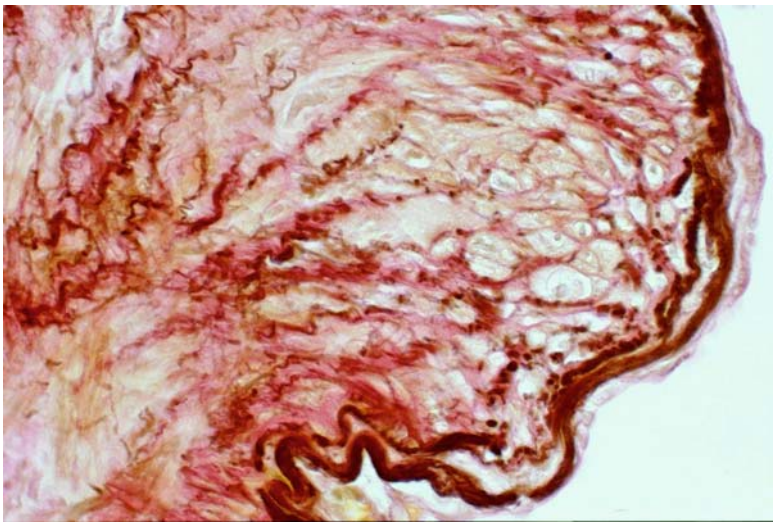


Fig. 5c) Internal carotid artery, elastica- van Gieson, 400x magnification

Detail of the internal carotid as shown above.

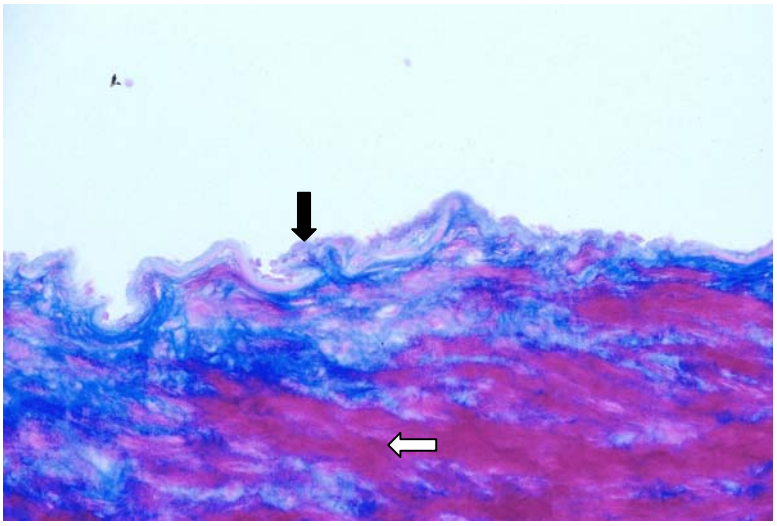


Fig. 5d) Internal carotid artery, Azan blue, 100x magnification

Detail with disruption of the internal elastic lamina (black arrow) and irregular SMC proliferation (white arrow).

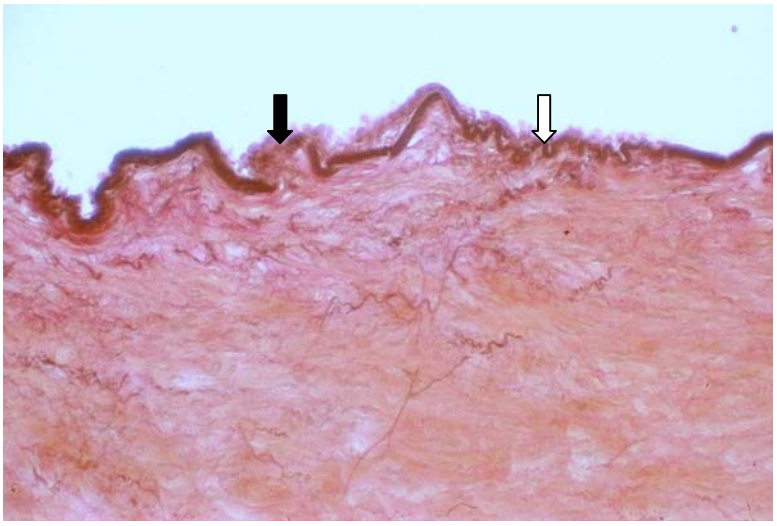


Fig. 5e) Internal carotid artery, elastica- van Gieson, 100x magnification

Detail as seen above with simultaneous reconstruction (white arrow) and destruction of the IEL (black arrow).

Case Six (male, 59 y)

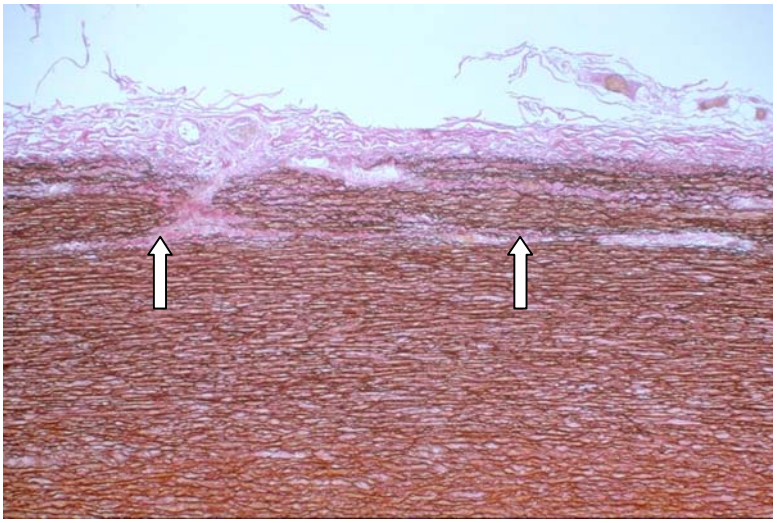


Fig. 6a) Aorta, elastica- van Gieson, 40x magnification

Aortic wall with intramural vasa vasorum (white arrows)

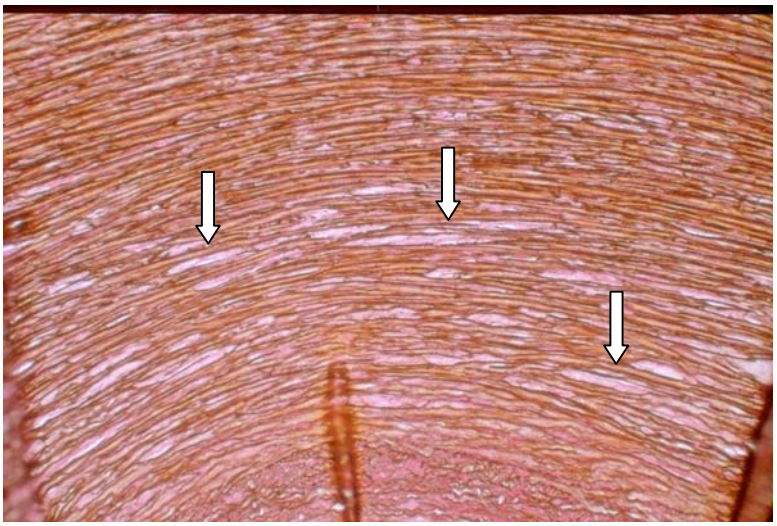


Fig. 6b) Aorta, elastica- van Gieson, 100x magnification

Aortic wall showing typical mucoid media degeneration with mucoid ground substance spreading atrophic elastic fibers apart (white arrows).

Case Seven (male, 26 y)

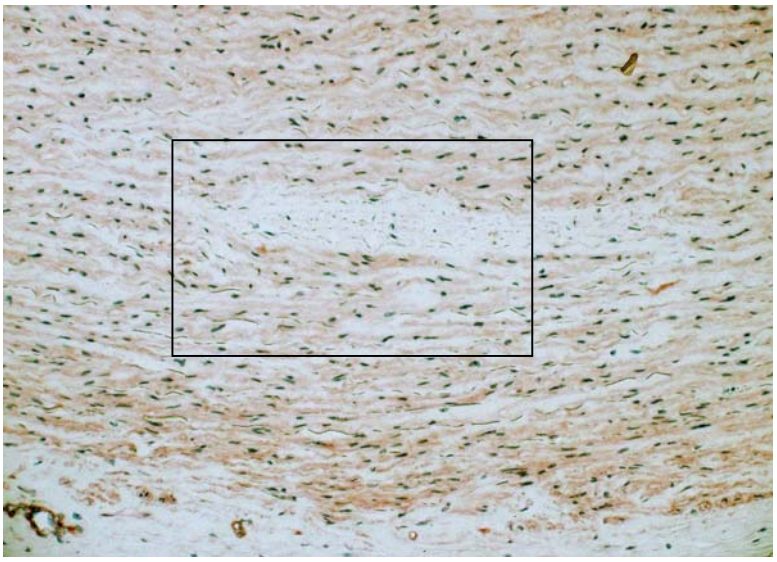


Fig. 7a) Common carotid artery, Collagen IV, 100x magnification

Cystic medionecrosis-like lesion with absence of basement membrane, loss of SMC and elastic fiber breakdown (see detail below).

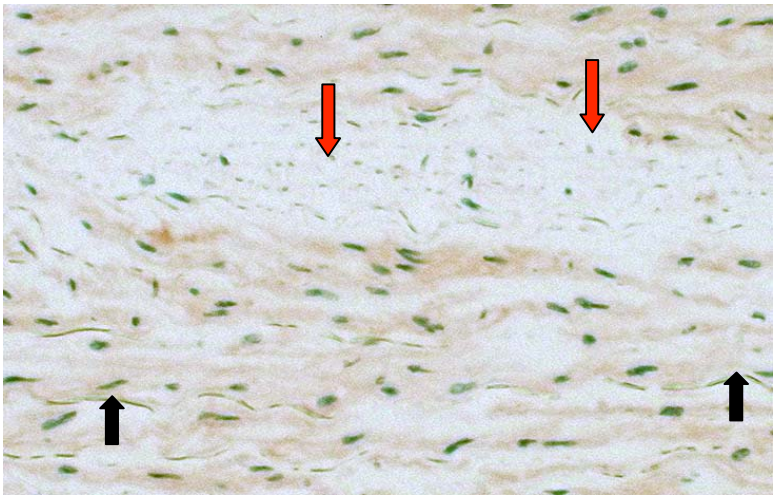


Fig. 7b) Common carotid artery, Collagen IV, 400x magnification

Focal elastinolysis seen as speckles in the lesion zone (red arrows), intact elastic fibers showing as translucent whitish-gray waved lines (black arrows). Absence of collagen IV stain in the pale lesion zone correlates with the paucity of SMC nuclei (dark gray).

6. Discussion

Our prospective histological assessment of macroscopically intact cervical arteries and aortic samples revealed medial changes akin to those described in association with spontaneous carotid and aortic dissection in 12.9% of our autopsy series. Prior dissection had occurred in 2 cases (3.7%) in cervical arteries. This is to our knowledge the first evaluation of a control series for cervical arteries.

In 1986, a histological study was performed on 34 aortic samples from dissecting aneurysms (99) to examine the matrix alterations. An unmatched control of 12 normal aortic samples was used for comparison. The main results were that the matrix composition in dissecting aortas differed from that of normal vessels in particular instances. Collagen IV (basement membrane) defects were present around SMC in cystic medial degeneration, mucoid degeneration and inflammation. Fibronectin defects were similarly located. The sites showing collagen IV and fibronectin reduction also showed elastin fiber fragmentation and intense but sometimes distorted staining for the interstitial matrix components collagen I and III. The conclusions were that hemodynamic conditions such as hypertension or turbulent blood flow damaged the basement membranes, and that reparative processes weakened the vessel wall and predisposed to dissection.

In a later ultrastructural and immunohistochemic analysis of a single case in 1997 (76), cystic medionecrosis and mucoid degeneration of the carotid artery was shown to be associated with a higher elastase content in the media and transformation of SMC from the contractile to the synthetic phenotype within the lesions. Yet later, in 2001, 22 aortic samples of patients with thoracic aneurysms, aortic distension due to valvular disease and dissecting aneurysms were studied (100) and examined immunocytochemically for reactivity to matrix

metalloproteinases and their inhibitors (MMP and TIMP) and ultrastructurally for morphometric aspects of SMC. The results showed that diseased vessels showed a much more pronounced reactivity to MMP-1 (collagenase), -2 and -9 and their inhibitors than did unaffected control vessels. Loss of SMC was of no importance in the development of vascular disease compared to the transition from the contractile to the synthetic/proliferative type with an increased production of MMP and changes in the intercellular and SMC- elastic fiber contacts (77,78).

Lesions found in dissected cervical arteries are usually similar to those in the aortic wall. Fibromuscular dysplasia is the only entity specific to muscular arteries. All these changes have in common an alteration of the medial wall that seems to be linked to the transition of SMC to a synthetic phenotype with the ensuing degradation of restraining matrix and elastic fibers to allow proliferation and increased secretion of growth-promoting matrix proteins.

In this series, the pattern alterations in the controls and the lesions observed in cases 1-7 all can be viewed as a manifestation of the SMC metabolic shift and its effect on the surrounding matrix and intercellular adhesions. The average ages at death of cases and controls were comparable, so that age-dependent changes would have affected both groups similarly.

Histoanatomy

The control vessels from the carotid bifurcation all showed transitional wall architecture with elements of both muscular and elastic arteries. As shown in figures B1 and C1, bands of elastic fibers were interwoven with bundles of SMC. Signs of focal SMC accumulations appeared in nearly all the observed internal and external carotid arteries. This rendered the appreciation of true pathological changes more difficult. The classification of a pattern alteration as pathological was often a matter of the degree of change. When analyzing histological samples from the carotid bifurcation not all divergences from “classic” layered

patterns are pathological, even highly developed whorls and irregular wall thickening in some cases are only a result of the continuous wall remodeling to maintain a certain level of laminar flow and shear stress. The wall opposite the divider is particularly subject to turbulence and low shear, and wall adaptations are more frequent. One should bear this in mind when interpreting photomicrographs for possible pathologic changes.

Differences between the inner, middle and external medial layer (Fig. 1) were visible in most vessels including the controls. Collagen IV and elastic fiber patterns were less clearly pronounced in the subintimal zone and collagen IV staining was always more clearly structured and intense in the subadventitial wall (Fig. A2, B1, F1, 2). SMC in the subintima were more often disordered, or arranged in whorls and knots beneath a fragmented internal elastic lamina, around weakened elastic fibers or beneath plaques (Fig. C1, D1, D2).

SMC in the subintimal media were more densely packed than in the middle or subadventitial level, and elastin fibers were more disordered and fragmented, lacking the layered or membranous organization they showed in the outer two-thirds of the media. This is in accordance with the assumption that the high density of SMC in the inner media coincides with a higher percentage of proliferative/synthetic-state SMC that produce elastase and thus continuously shape and disrupt their elastic matrix in response to activating signals from the endothelium. SMC in the internal media showed less consistent alignment along a common axis than did those in the central and external media. Considering that elastin membranes are instrumental in controlling SMC growth and their organization into concentric layers, it becomes clear that in order to proliferate, SMC must disengage from the surrounding elastin matrix. In a self-sustaining cycle, activated SMC degrade the elastic fibers, and the elastin degradation products in turn activate other SMC, providing the intima-media with a pool of recruitable cells for vascular remodeling and repair while at the same time removing the structural skeleton for ordered SMC alignment. It is easy to see

that this process needs to be finely tuned, and diseases such as FMD or intimal hyperplasia show the consequences of dysregulation.

Signs of focal elastinolysis (as opposed to the widely observed diffuse elastin fragmentation, resorption and disorganization) were found only in two individuals (Cases 6 and 7) in the subintima of the aorta or common carotid artery, where the elastic pattern was regular enough to spot focal lesions. These changes were not extensive or dramatic and did not seem related to age, BMI or cause of death or associated diseases. Vasospastic ischemia with hypoxic SMC reactions as a result of stress, hypertension or nicotine abuse may be at the root of focal elastin lesions.

SMC in the external media stained intensely but showed a different pattern than in the internal layer. They did not seem to degrade their matrix environment; rather one could observe an increase in structurally organized elastin and collagen. When vasa vasorum extended into the external media, SMC were more numerous in their vicinity but kept a structured arrangement and contractile phenotype as reflected by the intense and regular collagen IV staining. Some clusters of SMC around the vasa vasorum showed a circular or ovoid nucleus surrounded by a collagen IV stained ring. This would seem to indicate that the subadventitial perivascular SMC changed their alignment respective to the vessel wall to encircle the vasa vasorum.

SMC functions

The observation that connexin43 gap junctions (77,78) are dense in the SMC of the external media indicates that this is a region where cell-cell communication is of importance. In the vicinity to vasa vasorum, endothelial cells provide a certain amount of growth and signaling factors. In local and systemic immune processes, inflammatory mediators, cytokines and humoral factors acting on the EC can also exert their influence on the adjacent SMC. The subadventitial SMC are also in direct contact with sympathetic vascular nerve fibers and continually

produce NGF in a feedback loop with stimulatory neural input. These SMC can be activated and synthetic without proliferating, with a different function than the subintimal SMC. In effect, the vessel wall seems to show a bimodal functional and structural arrangement:

The subadventitial SMC, contractile and in contact with neural and endothelial inputs, would seem to act as the effector of central nervous and systemic demands on the vasculature, altering the vessel tone and vasomotor response according to need. The subintimal SMC would seem to fulfill a more local role, adapting the luminal profile in response to local alterations in shear, pressure and EC signaling. These SMC play a more important role in vessel wall metabolism, regulating transfer and absorption of fluids, nutrients and lipids, protecting the subadventitial SMC responsible for the vessel integrity, reactivity and vasomotor orchestration. The middle SMC would seem to function as a boundary layer between the two. Because of their location, the middle cells are shielded from external factors and retain their architectural integrity even when there is significant vascular alteration in the inner and outer layers. On the other hand, these cells are not in contact with blood vessels, and thus must be the most sensitive to ischemia and hypoxia, since they are furthest from both the arterial lumen and the vasa vasorum. Ischemia and hypoxia are therefore most likely to affect this region, leading to atrophy, apoptosis and necrosis. Unsurprisingly, it is this zone that shows the most thinning and cell loss under fibrous or atheromatous plaques (Fig D1, 2).

While the inner layer cells show richness of connexin43 gap junctions, as befits cells communicating incessantly, these gap junctions do not confer the same degree of tensile stability as tight junctions, which are more prevalent in the middle cell layers, where they can be observed as a band-like structure running lengthwise over the cell body (101). The SMC in outer layers have more gap junctions than the middle ones but are generally well anchored in the surrounding matrix proteins, providing good wall stability. In this case, the gap

junctions seem to serve not as channels for the organization of proliferation but rather as signal transducer channels for a coordinated vasoconstrictor response to neural input. The constant production of nerve growth factor must also be coordinated, and this is confirmed by experiments in which denuded SMC were able to attract nerve cell fibers by producing NGF and re-anchoring nerve fibers (83,84), recreating the structures necessary for coordinated vasomotor response. This difference in intercellular adhesion and grouping – recognizable in part by their ultrastructural arrangement in three different layers within the vessel wall – would explain why spontaneous dissection usually arises within the external or internal media, and only rarely in the central media.

Spontaneous dissection

Combining observations on the dynamic structure of the carotid bifurcation and current knowledge on vessel wall physiology, one can attempt to explain the risk factors for spontaneous dissection in the light of vascular wall architecture and functional diversity. All the risk factors known to predispose to spontaneous dissection affect either the original matrix composition (connective tissue diseases), increase the metabolic turnover of matrix protein within the vessel wall (pregnancy, hormonal treatment, infection) or damage the vessel wall and trigger the phenotypic shift of SMC (hypertension, sympathomimetics, stress, nicotine), or affect the vasomotion of the vessel wall and microcirculation (sympathomimetics, migraine, pregnancy). Most factors primarily affect the SMC, and it is the ensuing metabolic and proliferative shift that creates the conditions in which spontaneous or minimal-trauma dissection may occur.

It seems reasonable to distinguish two groups of individuals susceptible to spontaneous dissection. The first group includes people with apparent or inapparent connective tissue disease. These are generally at a higher risk of suffering vascular complications, as reflected in the earlier manifestation and higher recurrence rates of familial dissecting aneurysms (29,30,31). The second group comprises all those suffering acute or chronic stressors that affect the

immune and vascular system and trigger repair or increase matrix turnover within the media. These comprise all the other risk factors mentioned in part 3. Overlaps are of course possible, and so for instance a pregnant woman with Marfan syndrome and a history of cocaine abuse would probably be at a very high risk of developing vascular dissection.

On a microanatomic and physiological level, risk factors affect both the matrix composition and the behavior of SMC in the media. During pregnancy, especially the final trimester, an increase in collagen and elastin turnover is observed throughout the organism, including the blood vessels (46). It has been shown that the hormonal changes affect the polarization of vascular SMC, hyperpolarizing them and reducing the frequency and amplitude of spontaneous vasomotion. This adds to the increased peripheral fluid retention during pregnancy, since vasomotion is involved in recirculating tissue and lymph fluids in the vascular system. Vasomotion in the healthy artery is regulated by sympathetic innervation through vascular adrenergic fibers and Ca^{++}-dependent mechanisms.

Sympathomimetic agents influence the vasomotion of blood vessels, increasing the contractility and frequency, and can impair the blood flow in the microcirculation of the vascular wall. This would be in accordance with the observation that spontaneous dissections may occur after cocaine or amphetamine use. In this context it is interesting to note that the youngest case showing localized SMC and elastin degeneration had a history of cocaine abuse. In an artery weakened by defective matrix, increased matrix turnover, reduced SMC-matrix junctions, or a high population of proliferative SMC disengaged from the matrix network, increasing the contractile force of the alpha-actin positive, synchronized cells via sympathomimetics would exacerbate radial tension within the vessel wall. Intramural tension would easily force apart the vascular wall structures designed to resist pressure, not traction and cause microscopic tears.

Depending on their localization, vasa vasorum could be breached and then hemorrhage, expanding the tear and even rupturing into the lumen and opening the way for further dissection.

Conclusion

The vascular microanatomy of the carotid bifurcation is highly variable and any pattern changes should be interpreted with care since not all are indicative of vascular disease. Several types of lesions described in association with SCAD were found in this autopsy series, showing that these changes are not specific for SCAD but can present in individuals with no discernible vascular disease.

Vascular SMC, reacting to various stressors, undergo phenotypic transition from quiescent and contractile to proliferative and synthetic and alter their surrounding matrix, making the vessel wall more susceptible to dissection under particular circumstances in which viral infection, hormonal changes and enhanced sympathic activity seem to play a role. The superposed effects of intramural metabolic activity, immune cells, oscillating contractions and vasa vasorum need to be taken into account in order to understand the disease pathway. Subclinical connective tissue diseases are implicated in certain cases. Forensic institutes provide a generous source of material for vascular analyses to further the understanding of vascular wall adaptations and help elucidate spontaneous arterial dissection.

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8. Ehrenwörtliche Erklärung

Hiermit erkläre ich, dass ich die dem Fachbereich Medizin der Johann Wolfgang Goethe Universität zu Frankfurt am Main zur Promotionsprüfung eingereichte Arbeit mit dem Titel:

“Spontaneous carotid artery dissection-associated medial changes in a selected autopsy population”

im Zentrum der Rechtsmedizin der Johann Wolfgang Goethe Universität zu Frankfurt am Main, unter Leitung von Prof. Dr. H. Bratzke, ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation angeführten Hilfsmittel benutzt habe.

Ich habe bisher an keiner in- oder ausländischen Medizinischen Fakultät ein Gesuch um Zulassung zur Promotion eingereicht noch die vorliegende Arbeit als Dissertation vorgelegt.

Nathalie Frickey
Wien, den 7. Februar 2006

9. Curriculum vitae

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10. Danksagung

Ich bedanke mich vielmals bei Christine Elbert für ihre unentbehrliche Hilfe und Kompetenz bei der Anfertigung der histologischen Schnitte; bei Kathrin Yen und Constanze Niess für ihre Freundschaft, gemeinsame Whiskies an gewissen Tagen und ihre Hilfe bei der Probengewinnung. Meine besondere Dankbarkeit möchte ich meiner Familie, meinem Chef Prof. H. Bratzke und dem Mann meines Lebens Christophe Gilet ausdrücken für ihre unerschütterliche Geduld und Unterstützung, während diese Arbeit entstand.