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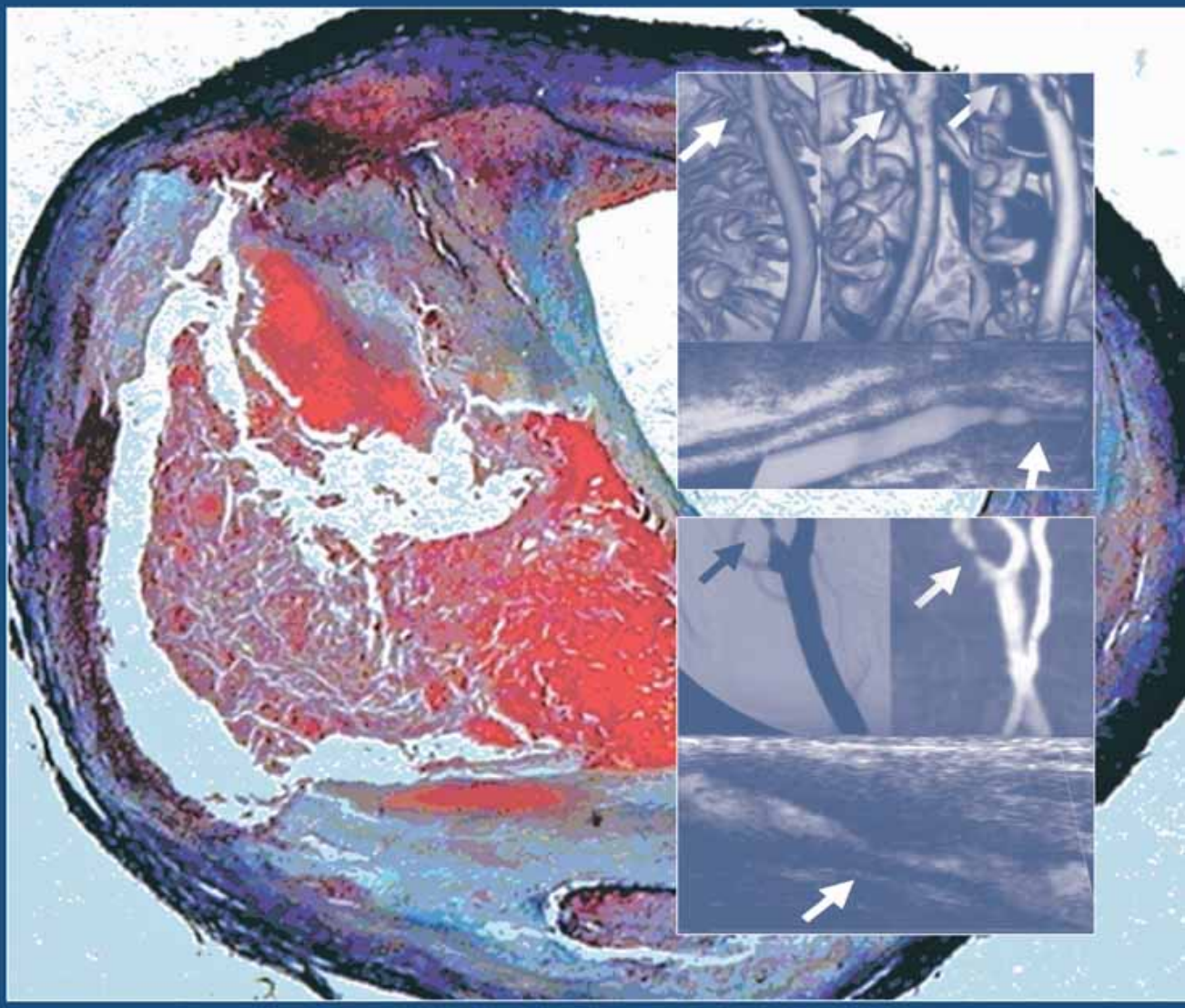
imaging of carotid artery stenosis



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Bernhard Schaller (ed.)

Imaging of Carotid Artery Stenosis

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INTRODUCTION

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"The most effective surgery is always that administered by the trained brain and hands of a surgeon" (M. G. Yasargil, 2005)

An adequate and state-of-the-art treatment of atherosclerotic disease of the extra- and intracranial carotid arteries in a patient with an advanced degree of stenosis substantially reduces the risk of subsequent ischemic stroke in patients with recently symptomatic 70 to 99% carotid artery stenosis. The benefit that is to be expected for 50 to 69% symptomatic stenosis, and for asymptomatic stenosis, is more modest [3]. Whether surgical endarterectomy, endovascular stent placement or any other treatment option proves to be the more effective treatment strategy of the narrowed carotid artery has not yet to be demonstrated. In any event, accurate assessment of the degree of luminal narrowing is an important step in the treatment planning. Conventional angiography was generally used to select patients for treatment in the past. However, given the risks of death and disabling stroke due to angiography (1.2% in the Asymptomatic Carotid Atherosclerosis Study [9] versus 1.1% for surgery itself), alternative noninvasive imaging techniques have been sought and investigated during the last years. There are several reasons for such a procedure: (i) the noninvasive methods are safe compared with conventional angiography, which still carries a mortality/morbidity rate of 1.2%, (ii) the noninvasive imaging can be done on an outpatient basis and is clearly preferred by patients and (iii) many physicians believe now that noninvasive imaging is sufficiently sensitive and specific to be used in at least some situations before endarterectomy.

Such new imaging methods necessarily provide more accurate results, and frequent re-evaluation of which methods are most efficacious is appropriate and necessary. The multimodal assessment of the plaque vulnerability involving the combination of biomarkers and these new imaging techniques that also target inflammatory and thrombotic components may be the best prerequisite to better understand the atherothrombotic risk and to be able therefore to better prevent ischemic stroke.

Any such investigation involving multi-technique imaging of the carotid arterial lumen rises the question of how meaningful are the comparisons made between modalities that are sensitive to the luminal area and those that assess the lumen diameter. Magnetic resonance (MR) angiography and computed tomography (CT) angiography provide images of the lumen in cross section, and Doppler sonography provides velocity measurements that are area-dependent, whereas conventional angiography, the historic "gold-standard" technique, is generally interpreted in terms of diameter measures.

Doppler ultrasound techniques are safe and relatively easy to perform, but when compared with angiography, they demonstrate only moderate sensitivity (65 to 87%) and specificity (71 to 91%) for detection of carotid artery stenoses that would be appropriate for surgery [1], [5]. Power Doppler [10] and contrast enhancement [8] are improvements, but ultrasound still cannot reliably differentiate high-grade carotid artery stenosis from occlusion, a critical factor in surgical and also non-surgical decision-making. Transcranial Doppler was limited therefore in the detection of intracranial carotid artery stenoses ("tandem lesions") by a high false positive rate [13], and was not possible in 15 to 20% of patients due to failure of ultrasound to penetrate the skull in the past.

MR angiography (MRA) is increasingly used in the neurovascular evaluation, especially with contrast enhancement [12], and may be improved by high-strength field gradients and high-resolution techniques. CT angiography (CTA) is still not used widely

enough to determine its effectiveness and, in any case, can only evaluate a limited segment of cerebral vasculature [6]. Because of its convenience and anatomic imaging qualities, there seems little doubt that CTA will become more widely used to screen for carotid artery stenosis and to assess patients with acute stroke and transient ischemic attacks. Technologic innovations will likely improve its imaging ability.

The choice of imaging strategy is also important in asymptomatic carotid artery disease. There is concern over the generalization of the results of the Asymptomatic Carotid Atherosclerosis Study, given the exemplary perioperative stroke/death rate of 2.3% seen in the trial, 1.2% of which was due to conventional angiography [2], [9]. Quoted surgical complication rates in asymptomatic case series range from 2.5% [7] to 5.6% [11]. Given these higher surgical complication rates seen in real-life clinical practice, the opportunity for patients to benefit from the procedure is further eroded by the inherent risks of angiography. Noninvasive imaging removes this additional risk to patients and may mean that skilled surgeons reach the 3.0% complication rate of stroke/death suggested by the American Heart Association for carotid endarterectomy to be appropriate for asymptomatic disease [4].

Despite these limitations, there is a growing tendency to rely solely on ultrasound or MRA/CTA in the presurgical assessment of patients with carotid artery stenosis. New and promising imaging techniques are additionally examined. Those capabilities should provide new opportunities for determining those image characteristics of the advanced atherosclerotic lesion that more comprehensively capture the complex nature of disease and more fully identify the true determinants of future neurological risk. The present book tries to give answers and proposals of solutions on some of these questions.

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IMAGING EXAMINATION TECHNIQUES OF CAROTID ARTERY

THE PATHOLOGY OF ATHEROSCLEROSIS

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Atherosclerosis is an indolent, chronic arterial disease involving inflammation and thickening of the walls of medium- and large-sized vessels, with potentially-lethal sequelae. An atherosclerotic lesion is an accumulation of lipids and inflammatory cells, within the arterial wall, which becomes more complicated and extensive and deforms the involved artery, with time. Clinically-significant lesions of atherosclerosis typically become manifest after decades of growth and transformation; yet, not all lesions become symptomatic and many end by becoming calcified or fibrotic, with no clinical significance. Atherosclerotic lesions of the carotid arteries begin in infancy [19]. The arterial response that *initiates* atherosclerosis has not been definitively identified [63]. Yet the subsequent natural history of atherosclerosis has been well-characterized. The vascular burden of atherosclerosis increases in volume and extent, over decades, remaining clinically 'silent', while progressing through stages of development, with changes in the morphology and composition of lesions. Atherosclerotic lesions, known in advanced stages as 'atheroma' or 'plaques', may expose 'thrombogenic' substances or become bulging plaques that obstruct blood flow through the carotid, causing local 'hypercoagulability'. Such thrombogenicity and hypercoagulability may provoke the local formation of a blood clot, or 'thrombus', in the lumen of the carotid artery. Thrombi which are so formed may become fragmented, forming 'emboli'. Thromboembolism, or downstream circulation of blood clot fragments, from carotid atheromata, can cause frightening neurological symptoms and permanent damage of the brain, or stroke, when emboli lodge emboli in smaller vessels, blocking blood flow to vital neurological tissues downstream.

Clinicians caring for patients with carotid atherosclerosis are unable to monitor disease-progression or predict the occurrence of sequelae to any reliable degree by physical examination and history alone. Medical imaging modalities, in particular ultrasound and magnetic resonance imaging, have given clinicians the ability to examine the carotid arteries non-invasively [68], to identify and monitor the growth of atherosclerotic lesions, evaluate the adequacy of carotid blood flow, and detect thrombus formation. Regrettably, imaging cannot predict the efficacy of pharmacotherapy or lifestyle-interventions on atheroma; identify patients who will benefit most from invasive carotid procedures (except in limited circumstances [9]); or identify atheroma most likely to provoke a dire vascular event – so-called 'vulnerable' or unstable plaques.

A major goal of non-invasive radionuclide vascular imaging is to supply clinicians with these capabilities. Current medical imaging of carotid atherosclerosis provides information about the morphology of the lesion, while new techniques, interrogating the cellular composition of the lesions, are likely to identify factors that promote plaque instability.

Atherogenesis

The *response to injury hypothesis* [51], [32] proposes that an injury to the endothelium exposes the underlying vessel wall, triggering a vascular response which, rather than being reparative, results in an atherosclerotic lesion. The precise nature of this initial dys-response, the ultimate cause of atherosclerosis, or atherogenesis, remains a mystery. Yet the formation and propagation of atherosclerotic lesions, is increasingly well-understood to involve dyslipidemia and inflammation [32], [14].

Atherosclerosis is common, detected even in the arteries of healthy young people, in their second or third decade of life [36], and has even been found in the newborns of hyperlipidemic mothers. Yet atherosclerosis does not manifest itself clinically until much later in life. The symptoms are due to decreased perfusion distal to the atheroma, due to the flow limiting stenosis in a major vessel such as a carotid or coronary artery, or to a pathological expansion of the diameter of an affected segment of artery, as in abdominal aortic aneurysms (AAAs). These two types of arterial 'remodeling' can overlap, as, for example, an outward enlargement of coronary lesions precedes narrowing of the lumen [20] in atherosclerosis of the heart. Atheromata develop in stages, with years of silent progression leading up to an event, such as a transient ischemic attack or stroke. In the early stages, atheromata accumulate lipids, such as low-density lipoproteins (LDL), between the endothelium and intima/media of the vessel. The endothelium is a single layer of cells, which lines the inner surface of blood vessels. The endothelial cells communicate with other cells in important ways, as will be discussed.

Traditionally, lipids are thought to enter atherosclerotic lesions by diffusion from the lumen, diffusing through the inner layers of the vascular wall. Yet, atheroma may also gather lipids from the vasculature of the vessel itself, the *vasa vasorum*. In growing atherosclerotic lesions, the number of vessels in the vasa vasorum is increased, in response to the inflammation in the lesion, and these proliferating vasa are fragile and permeable. These fragile vessels can rupture, leading to intramural hemorrhage, or may allow small amounts of plasma and red cells to extravasate. When this occurs, the plasma membranes of the extravasated erythrocytes provide atheromata with a rich source of additional lipids and cholesterol [29], leading to further growth of the lesion. Inflammation caused by the atheroma leads to macrophage recruitment. The macrophages attempt to ingest and digest the lipid, which leads to increased metabolism on the part of the cells, and creation of a local environment conducive to oxidation of LDL in the area. While non-oxidized LDL cholesterol is a normal component of the arterial wall, oxidized LDL is extremely irritating, contributing to local inflammation in the lesion.

Oxidized molecules accumulate in atheroma, often in association with an undersupply of antioxidants in the microenvironment [59], [35]. The excess of oxidants in vascular cells puts an 'oxidative stress' on the vessel wall which promotes atherosclerosis by impairing endothelial cell function and oxidizing LDL [59], [35].

The hostile microenvironment of inflammatory cells provokes the overlying endothelium to release cytokines and growth factors which stimulate the growth of smooth muscle cells (SMCs), degrade the extracellular matrix of the atheroma, and invite additional inflammatory cells into the lesion, from the blood. As lipid-laden macrophages, or 'foam cells', accumulate and SMC proliferation continues, the atheroma grows.

Predispositions to atherosclerosis

Patients with a family history of atherosclerotic disease are at higher risk of developing significant atherosclerotic disease, and several genes have been associated with worse manifestations of atherosclerosis [18]. The genes which transmit a heritable trait of susceptibility to worse forms of atherosclerosis do not follow simple Mendelian patterns, and atherosclerotic susceptibility is likely the result of multiple genes. For example, progression of atherosclerotic lesions is associated with 'remodeling' of the microenvironment of the lesion, including degradation of the extracellular matrix, by the family of matrix metalloproteinases (MMPs). Abnormal polymorphisms in the genes for MMPs-3 and -9 have been identified, in patients suffering from more severe atherosclerosis. Similarly, a large number of genes control plasma levels of lipids, such as LDL cholesterol, HDL cholesterol, triglycerides and lipoprotein (a) (reviewed by [4]) which, typically in conjunction with diet, can play key roles in atherogenesis. Preliminary research into genetic alterations affecting inflammatory biomolecules, such as CRP, various interleukins, chemokines and Toll-like receptors (reviewed by [4]) suggest a heritable risk in the inflammatory component of atherosclerosis, as well.

Gene therapy is being explored to correct the imbalances of gene expression at sites of disease or at one or more organ sites to effect systemic changes. For example, in carotid atherosclerosis, local gene transfer to the arterial wall may be employed to inhibit restenosis after carotid vascular interventions, or stabilize vulnerable plaques; or gene transfer may seek to produce systemic changes in lipoprotein metabolism, for example, by targeting metabolic genes in the liver.

Recent research implicates the aging of the endothelial layer in the progression of atherosclerosis. Endothelium is subject to injury and must be able to replace lost endothelial cells. Recent data suggests that, as people age, endothelium becomes *senescent* , losing its ability to regenerate after injury. This observation adds a maladaptive healing *response* to injury as an age-related cause of atheroma.

Young blood vessels reconstitute defects in the endothelial layer through the formation of new endothelial cells by *proliferation* of neighboring vascular endothelial cells, or the recruitment of endothelial progenitor cells (EPCs) which circulate in the bloodstream after being formed in the bone marrow. During life, endothelial cells and the marrow precursors are called upon to divide, creating new (duplicate) cells. With each cell division, the length of chromosomal telomeres becomes shorter, called *telomeric attrition*. Telomeres are repetitive nucleotide sequences found at the end of chromosomes, crucial for DNA replication and stability. The more often an endothelial cell divides, the more its chromosomal telomeres shorten. Radioautographic studies show a higher rate of turnover of endothelial cells overlying atherosclerotic lesions than cells in normal endothelium. Once telomere length shortens to a critical threshold, endothelial cells will no longer divide, a state known as *senescence*. Senescent endothelial cells have been found covering plaques, in autopsy studies of adults [39].

Endothelial senescence likely plays an important role in progression of disease but is unnecessary for the initiation of atheroma since fatty streaks can be found in the aortae and carotid arteries of healthy infants [19], before telomere attrition would reasonably occur. However, injury to the endothelium accelerates endothelial senescence and, therefore, may contribute to the development of carotid atherosclerosis in younger patients exposed, for example, to carotid balloon injury or neck irradiation. Progression of atherosclerosis, in the aged, is also associated with changes in sex hormones, in both men and women.

The prevalence and extent of atheromata is increased by cigarette-smoking [37], hypertension, diabetes, and specific genetic diseases [4]. In carotid atherosclerosis, cigarette-smoking has been shown to increase intralesional macrophage content, with an associated increase in intralesional inflammatory enzymes (i.e., macrophage-derived metalloelastase) which degrade vascular tissue.

Morphology

Atherosclerotic lesions have traditionally been analyzed in terms of histology; the progression of a plaque is commonly-rated according to its histological structure and composition [65]. In youth, atherosclerotic lesions are frequently composed of 'fatty streaks' [10]; the prevalence of such lesions plateaus after the first three or four decades of life, whereas raised plaques, more advanced forms of atherosclerosis, continue to accumulate until the end of life. An 'advanced' atherosclerotic lesion is commonly called either an 'atheroma', after the Greek words *athere,* for 'porridge', and *oma,* for tumor (referring to the swollen appearance of the lesion,) or a plaque, denoting its raised morphology (see discussion of atherosclerosis terminology below). A formal definition of an 'advanced' atherosclerotic lesions has been given as one in which in the layer of the blood vessel wall immediately adjacent to the vascular lumen, or *intima*, has become thickened and disorganized and the artery deformed [62]. Plaques are often associated with complications, on or immediately beneath the luminal surface, in the 'cap' of the lesion, such as fissures, ulcerations, and ruptures (*see below*). Deposits of hematoma, or intraplaque hemorrhage, and thrombosis may become incorporated into plaques as fibromuscular tissue [65].

The American Heart Association (AHA) proposed a formal system of histological classification, of early versus advanced atherosclerotic lesions, using a

numerical nomenclature (see Fig. 1), and recommended the use of such classifications as "histological 'templates' for images of lesions . . . obtained with a variety of invasive and noninvasive techniques" [65].

The arrangement of lesion-types, from I to VIII, is intended to reflect the natural history of atherosclerosis and distinguishes lesions associated with adverse clinical manifestations (types IV–VIII) from lesions without such potential (types I–III) [62]. In what is generally-regarded as early forms of atherosclerosis (types I–III) [63], endothelial injury exposes the intima to deposition of a small amount of lipids, inciting a local inflammatory reaction populated by macrophages. In early-stage lesions endothelial integrity is usually intact, although, in animal models of aggressive atherosclerosis, it can be focally-disrupted, with platelets bound to exposed foam cells [12], [13]. The endothelium overlying lesions undergoes other changes, even at early stages, including a loss of alignment to blood flow, increase in stress fiber content, and an increased susceptibility to adherence by circulating leukocytes, thought to be due to increased endothelial expression of specific adherence molecules like vascular cell adhesion molecule-1 (VCAM-1).

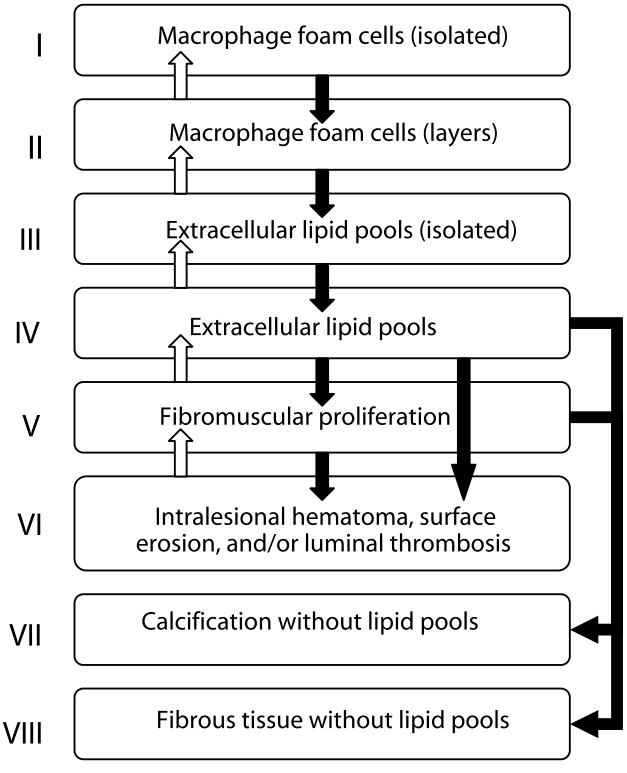

Fig. 1. An outline showing the AHA-recommended numerical classification of atherosclerotic lesions, with roman numerals and predominant histological characteristic(s). Arrows indicate possible changes in the histology of atherosclerotic lesion at different stages. Modified from [65].

Injury exposes the vessel wall to the deposition of circulating lipids. Infiltrating macrophages ingest the lipid deposits, becoming *foam cells,* and secrete growth factors and pro-inflammatory molecules (eg, matrix metalloproteinases, and possibly myeloperoxidase [38]) that perpetuate and amplify local inflammation, e.g., by oxidation products (see below). Initially, atheromata are no more than yellow dots (type I) on the vascular surface, composed of foam cells. As foam cell groups expand into layers (type II), sometimes visible as streaks, smooth muscle cells begin accumulating lipids, mostly cholesterol esters, though a surplus of lipid-free macrophages are present. Mast cells and T-lymphocytes also arrive, but in far fewer numbers. In 'pre-atheroma' (type III) lesions, lipid begins accumulating in small 'pools', outside of cells, but not to a large extent; and the lipids are of a different mixture than in prior stages, including more free cholesterol [60].

The term 'atheroma' is commonly used to refer to all advanced lesions (types IV–VIII) which are distinguished by (1) accumulations of lipid, cells, and/or matrix components, including minerals; (2) intimal disorganization, repair, and thickening; and (3) deformity of the arterial wall [62]. 'Atheroma' originally referred to the type IV lesion, which has a large 'core' of confluent extracellular lipid pools. **Type IV** atheromata expand by growth of the lipid core, but usually away from the lumen, so-called Glagovian expansion [20]. This type of lesion rarely occludes blood vessels [65]. The type IV atheroma has a normal '*cap*' – i.e., intimal tissue found between lesion and endothelium is normal [64]; though the cap can be relatively-thick, at characteristic arterial sites, as an adaption to mechanical forces, its composition is that of normal intimal tissue. Yet inflammatory macrophages are abundant, in the periphery of type IV atheromata. The

integrity of the cap is important, since 'fissures', 'ulcerations', or 'ruptures' of the cap can provoke vascular thrombosis [74]. Thinning of the cap is also more frequent in symptomatic than in asymptomatic carotid plaques [5]. Having well-maintained caps, type IV atheromata are rarely associated with vascular events [65], unless type IV lesions become type VI lesions (see below). **Type V** lesions, once called 'fibroatheroma' are distinguished by an increased amount of smooth muscle cells, in the intima, and fibrous tissue, mostly notably in the cap, with persistence of a fatty lesion core. The fibromuscular tissue arises during repairs of intima from damage caused by the extracellular lipids or thrombotic deposits. The term 'plaque' was initially intended to denote the fibrous cap of type V lesions [62]; however, like 'atheroma', 'plaque' has become indiscriminately-used to refer to all types of advanced atherosclerotic lesions. Repeated repair episodes are the presumed cause of multi-layered (type V) lesions. As each new layer forms, the tough fibrous tissue of underlying plaque-layers forces the lesion to expand by growing into the lumen of the artery. The layer outside of the intima, the media, and the outermost vascular layer, the adventitia, both demonstrate changes, in composition, in type V lesions. For example, the smooth muscle cells are disorganized, in the media, and both the media and adventitia accumulate inflammatory cells, including macrophages, lymphocytes, and, sometimes, mast cells. The lipid pool may persist, in type V lesions, or be absent, though inflammatory cells persist regardless. For the first time, calcifications are sometimes seen. A **type VI**, or complicated, lesion is marked by the occurrence of (1) erosions or fissures on the surface of the lesion, whether superficial, involving only the endothelium, or deep, down to the lipid core; (2) hematoma, blood collections within the lesion, which may form by tears in the surface of the lesion and/or rupture of lesional microvessels formed during angiogenesis (see below) [1], [47]; and/or (3) thrombosis, on the surface of the lesion, which can be microscopic or grossly-visible [7]. Type VI is the lesion-type most often associated with clinical manifestations, including lethal ones [65]; hemorrhage-laden type VI lesions are likely to increase in volume, expand their necrotic lipid cores, and develop recurrent intralesional hemorrhages, from year to year [67]. As lesions become advanced, apoptotic cells begin accumulating, particularly around the necrotic lipid core [24], [27], [69]. In part, apoptotic cell-accumulation can be attributed to the increasing oxidative stress, in advanced lesions, which interferes with the phagocytosis and clearing functions of infiltrating macrophages [58].

As illustrated in Fig. 1, type VI lesions arise from lesions of either type IV or type V. A type VI lesion can worsen, leading to thrombotic occlusion of the carotid artery, or repair itself, becoming a type V lesion. Not all type VI lesions have acute consequences or will necessarily become clinically-manifest, nor are such lesions even uncommon in the arterial tree; for example, type VI lesions have been found in young adults [61] and in the aortae of 38% of adults below the age of 60 years [7]. Yet, in carotid atherosclerosis, plaque disruption is associated with symptomatic disease, even between lesions with similar degrees of stenosis [5].

Should the lipid core of a type IV–VI lesion regress, either calcification (**type VII**, or calcific, lesion) or fibrous tissue (**type VIII**, or fibrotic, lesion) will predominate, replacing normal intimal tissue [61]. Lastly, the histology of a specific atherosclerotic lesion most often varies, along its extent (e.g., a lesion may demonstrate type II features, in one area, and type V, in another); yet, in pathology, atherosclerotic lesions are classified according to the most advanced and clinically-significant intralesional histology present.

Causes of plaque 'vulnerability'

Acute vascular events associated with atheroma do not require exposure of thrombogenic substances, since thrombi may form on the surface of lesions with intact endothelium. The hypothesized etiology of thrombosis in such cases is a focal change in blood flow secondary to deformity of the vessel overlying a lesion. Thrombotic occlusion tended to occur at flow dividers and locations of arterial angulation [66], suggesting a role for shear stress in thrombosis or underlying intimal disruption and hematoma and a reason for the predilection of atherosclerosis at the carotid bifurcation [45]. Another factor in the devel-