# Atherosclerosis: Clinical Perspectives Through Imaging

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*Dedicated in recognition of the many men and women who proudly and selflessly contributed to the advancement of medical science and who served their country at Walter Reed Army Medical Center, 1909–2011*

# Foreword

Advances in medical imaging technologies continue to drive new knowledge in the field of atherosclerosis. Research continues to push the limits of the acuity and accuracy of medical imaging, allowing us to understand more about cardiovascular anatomy, function, and interrelationships with other organ systems.

As with many areas of medical research, advances in atherosclerosis imaging have experienced crystalline growth, where knowledge resulting from one avenue of development has spurred further growth in others. Within the past decades, we have learned a great deal about the anatomical, functional, and molecular changes in atherosclerosis. Atherosclerotic plaques do not simply increase in size to produce clinical symptoms, but factors influencing plaque burden, inflammation, vascular reactivity, and lesion stability intertwine to produce an assortment of possible adverse clinical consequences. Further explosions in disciplines such as molecular medicine, proteomics, genomics, metabolomics, and nanotechnology have confirmed and refined this knowledge and have led to further advancements in imaging capabilities, particularly in the area of molecular imaging. It is generally accepted that vessels do not only influence their own local environment, but that they have effects on end-organ pathobiology. Through the use of non-invasive serial imaging such as is possible with magnetic resonance imaging, we may be allowed some insight into the characteristics of vessel wall disease that result in disease progression, complication, and symptoms. Positron emission tomography/computed tomography imaging is now able to evaluate metabolic activity in plaques, which is believed to be an important predictor of future plaque rupture. Therefore, it may be possible to use these tools to develop new prognostic markers to guide novel targeted therapies.

The array of available imaging tools now available is a testament to remarkable medical innovation, but also belies the fact that no single tool is a perfect window. Therefore, the advantages and disadvantages of each modality must be well understood and applied to the appropriately selected patient under the appropriate circumstances. Invasive coronary angiography has become a staple in the diagnosis of coronary artery disease in individuals and for identifying discrete lesions requiring clinical intervention. Some of the limitations inherent in this two-dimensional silhouette imaging of the lumen have been overcome by the use of intravascular ultrasonography. Intravascular ultrasound imaging of the coronary arteries requires more advanced equipment and technical skill, but the resulting advantages of visualizing three-dimensional

vascular structures including both the lumen and arterial wall as well as the ability to detect small changes in plaque burden over time in randomized controlled clinical trials represent more than a fair trade. Yet the invasive nature of both traditional coronary angiography and intravascular ultrasound remains, but this invasive nature may eventually be overcome through the refinements in non-invasive coronary imaging.

Additionally, as rapid advances are made in each technology, the standardization as well as training and transfer of information become vital. This applies both to the acquisition of images and also to the interpretation of the images upon which so many important decisions rest. Therefore, it is also critically important to develop the next generation of imaging scientists and clinical imagers who will work together to identify gaps and move imaging toward more broad clinical application and standardization. This volume is an important step toward that goal.

The expert editors and authors provide the reader with a clear description of atherosclerosis and its pathogenesis, allowing for a complete understanding of how best to apply imaging in a variety of different settings. Chapters dedicated to individual imaging technologies ranging from invasive modalities including coronary angiography and intravascular ultrasound to noninvasive imaging using carotid ultrasound for measurements of intima-media thickness, cardiac computed tomography, coronary computed tomography angiography, magnetic resonance imaging, and positron emission tomography provide information in a format that is both relevant and complete. Together, these chapters form a comprehensive, practical, state-of-the-art imaging manual that is well-suited for trainees as well as experienced professionals.

Jean-Claude Tardif, M.D.
Therese Heinonen, DVM

# Preface

Atherosclerosis represents the root cause of stroke, heart attack, heart failure, and sudden cardiac death account for over one in four deaths in the United States for both men and women. The problem affects the young and the old, with over ¾ million first heart attacks occurring each year. Lastly, the annual costs of coronary heart disease alone exceed $100 billion. A large number of risk factors for atherosclerosis have been identified. Typical risk factors such as aging, hypertension, hyperlipidemia, diabetes mellitus, tobacco use, physical inactivity, and diets high in saturated fat contribute to the development of atherosclerosis, although, interestingly, these factors explain only a minority of atherosclerosis. A large number of other factors ranging from genetics to lipid alterations to novel factors may add further to the sum of atherosclerosis, but ultimately clinicians are faced with a difficult task of predicting who will and who will not develop atherosclerosis and one of its consequences during their lifetimes. Furthering the detection problem, atherosclerosis is nearly universally present in middle-aged adults to at least some degree of severity, becoming increasingly prevalent with age. This raises the problem of having detection techniques with capabilities beyond simple detection, but with quantitative characteristics for determination of disease severity.

How do we get beyond the problem of probabilistic detection of atherosclerosis risk? Imaging provides the "Sutton's Law" for atherosclerosis. Asked why he robbed banks, the (somewhat) legendary Willie Sutton replied, "Because that's where the money is." Imaging provides the opportunity to extend the clinical perspective of atherosclerosis beyond predictive models to direct assessment, thereby removing uncertainty in its detection. The field of atherosclerosis imaging began with attempts to image coronary artery calcium with standard radiographic techniques such as fluoroscopy in the 1970s and 1980s. The key moment propelling the field forward was the advent of electron beam computed tomography in the early 1990s. The conceptual approach of electron beam CT forms the foundation for the field: to identify and quantify atherosclerosis, leading to the reflective axiom that, once found, the treatable root causes of atherosclerosis must be targeted through cardiopreventive strategies. Now, two decades into the field of atherosclerosis imaging, new techniques have emerged, and several techniques have entered mainstream practice on the basis of their clinical impact. Methods of atherosclerosis assessment range from the most simple (predictive tools and clinical examination) to broadly available (cardiovascular CT and ultrasound) to leading edge techniques (nuclear imaging, positron emission technology, and cardiovascular

magnetic resonance imaging). Although these methods vary in the aspects of atherosclerosis they target, the fundamental underpinning of each is to provide an accurate, clinically-relevant assessment of atherosclerosis.

This handbook provides a practical, clinically-oriented approach to the use of atherosclerosis imaging techniques in clinical medicine. The book is intended for clinicians of all interests who evaluate patients at risk for coronary heart disease, from family practitioners, internists, and nurse practitioners to cardiovascular specialists. Chapters focus on individual modalities, providing a detailed description of the imaging method, its quality performance, and its characteristics for the quantification and accuracy for the detection of atherosclerosis. Numerous imaging examples visually orient the reader to the practice of atherosclerosis imaging. For all methods, details of the data supporting their use in the diagnosis and prognosis of coronary heart disease show that the methods range from clinically mature, enabling their endorsement in guideline statements (e.g., carotid intima media thickness testing, coronary artery calcium assessments), to highly developmental. Finally, the methods are considered within their capability for serial assessments for atherosclerosis monitoring. Important distinctions among the different techniques include the use of ionizing radiation, the specific components of atherosclerosis targeted (e.g., inflammation or calcium), and whether they can be provided as an office or facility-based technique (e.g., ultrasound versus magnetic resonance imaging).

Atherosclerosis has emerged as a disease process worthy of specific focus for its detection and treatment. Now, with the advent of so many techniques for its direct assessment, the field is poised to rise from the shadows of probabilistic medicine to one in the future in which the direct measurement of atherosclerosis will be commonplace. Much like age-mandated screening for breast cancer with mammography or colon cancer detection with colonoscopy, imaging will provide the means for early detection and efficient targeted management of patients with evidence-based treatment approaches. Thus, the dawning of the emerging field of "atherosclerosis-ology." The field represents an opportunity for all to embrace atherodetection with techniques from the simple to the high tech. We sincerely hope this handbook provides a useful primer for thoughtful clinicians of all interests to valuably increase their practical understanding of atherosclerosis imaging, enabling them to broaden their skills in this emerging field.

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# Part I

# Basics and Clinical Atherosclerosis

# Insights into the Natural History of Atherosclerosis Progression

1

Masataka Nakano, Jacob Stephen, Miranda C.A. Kramer, Elena R. Ladich, Frank D. Kolodgie, and Renu Virmani

**Abstract**

Pathology of high risk atherosclerotic plaque provides the basis for understanding the imaging and treatment of atherosclerosis. The earliest vascular change described microscopically are adaptive intimal thickening and fatty streaks, whereas pathologic intimal thickening are the first of the progressive plaques subtypes. Fibroatheromas are characterized by an acellular necrotic core, accumulated cellular debris and cholesterol monohydrate, and a lack of extracellular matrix. The development of the necrotic core is believed to originate from apoptotic macrophages. Thinning of the fibrous cap leads to plaques vulnerable to rupture, or thin-cap fibroatheromas. Overlying thrombosis can arise from one of several mechanisms including ruptures, erosion, or calcified nodules. Calcium within atherosclerosis is a common imaging target which increases with lesion progression and is present in greatest frequent in healed plaque ruptures and fibrous plaques. Thin cap fibroatheromas most frequently contain speckled calcification but may show heavily calcified areas or an absence of calcification. which is not very useful in diagnosing these lesions by calcium-based imaging. Coronary lesions with thrombi in the absence of rupture (erosions) exclusively show stippled or no calcification. Rupture in the absence of calcification is rare. In contrast, diffuse calcification is almost always associated with healed ruptures.

**Keywords**

Pathology • Atherosclerosis • Vulnerable plaque • Thrombosis • Calcification

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## Background

- Atherosclerosis is a complex disease with a multi-factorial etiology related to inheritance, and traditional and nontraditional risk factors. Despite major medical advances in the treatment of atherosclerosis, approximately two thirds of patients remain refractory to statins, one of the most successful agents targeted for the prevention of myocardial infarction. The lack of a more substantial treatment effect underscores the limitations of lipid lowering monotherapy and emphasizes the complexity of the disease and requirement for multi-targeting of other critical processes. Moreover, despite the rapid progress in newer and refined imaging modalities that can image atherosclerosis, the inability to completely characterize atherosclerotic lesions in individual patients presents another important issue. Therefore, advancing the field is contingent on a better understanding of the morphologic characteristics of high-risk plaques in living patients, who harbor the capability of producing symptomatic events. Insights into how critical elements influence lesions stability primarily involve:
  - macrophage foam cells
  - necrotic core size
  - fibrous cap thickness
  - neoangiogenesis/hemorrhage
- Any advancement(s) towards designing therapies targeted at plaque stabilization will likely require the identification putative pharmacologic agents and clinical refinements to validate and monitor treatment effects, potentially with arterial imaging techniques. Finally, a better understanding of the temporal relationship between active and healing lesions is needed to recognize the natural changes in plaque composition caused by silent or symptomatic events.
- While intensive research has lead to a few breakthroughs in preventative therapies such as lipid lowering, most mechanistic insights are yet to be translated into new treatments. This limitation partly exists since the precise causes(s) of lesion progression from asymptomatic stable fibroatheromas into high-risk plaques for rupture (thin cap fibroatheroma or vulnerable plaque) are incompletely understood.

## Natural progression of atherosclerotic plaque in humans

- In animal models of atherosclerosis, hyperlipidemia-induced macrophage infiltration of the intima, constitutes one of the earliest pathologic changes [1], which can be reversed if the dietary cholesterol intake is reduced and/or circulating cholesterol is decreased by pharmacologic means. As an endpoint, however, advanced animal lesions have limited resemblance to man since findings of luminal thrombi attributed to rupture are rare [2, 3]. Nonetheless, early atherosclerosis in humans is recognized in all populations irrespective of the presence of risk factors as early as the first decade [4].
- Atherosclerotic lesions have been extensively studied at autopsy where specific plaque morphologies have been assigned to categories established by the American Heart Association consensus group, lead by Dr. Stary in the mid-1990s [5, 6]. Our laboratory subsequently modified this classification as the cause of coronary thrombosis is not exclusive to rupture as implied by the AHA, but alternatively includes erosion and eruptive nodular calcification. In addition, the thin-cap fibroatheroma, the assumed precursor lesion to rupture (vulnerable plaque), was also introduced since this definition is also missing in the AHA classification.

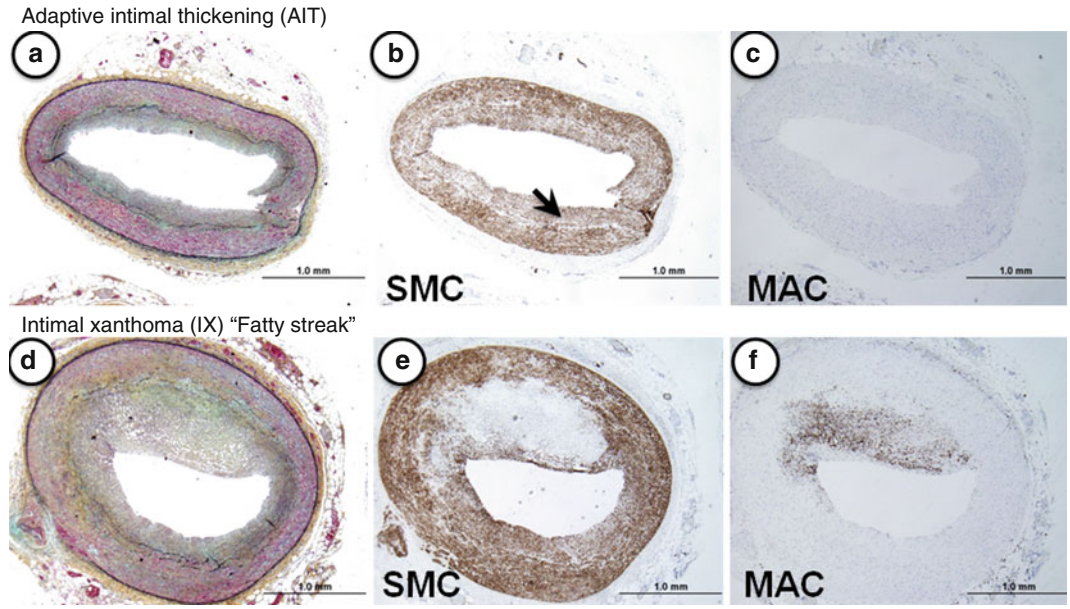


**Fig. 1.1** (**a**–**f**) Lesion morphologies consistent with non-progressive atherosclerosis. (**a**–**c**) Adaptive intimal thickening (*AIT*). Normal coronary vessel with a thin smooth muscle-rich neointima (**b**, α-SMC actin immunostaining, *arrow*). Note the absence of lesional macrophages (*MACs*, **c**). (**d**–**f**) Intimal xanthoma (*IX*) or so-called "fatty streak." Serial sections of the same eccentric plaque show few α-actin positive SMCs (**d**), while CD68-positive macrophages are very prominent (**f**)

## Atherosclerotic Plaque Morphologies

### Non-progressive Atherosclerosis
(Fig. 1.1a–f)

- The earliest vascular change described microscopically is adaptive intimal thickening (AHA Type I), which is found in at least 30 % of neonates at birth. The next category represents fatty streaks (AHA Type II), which are characterized by non-raised lesions consisting of intimal macrophages with intra- and extracellular lipid deposits. These lesions tend to regress in certain locations, e.g., thoracic aorta and the mid right coronary artery [7].

### Progressive Atherosclerosis
(Fig. 1.2a–f)

- Our laboratory recognizes pathologic intimal thickening, also known as the intermediate (AHA Type III) lesion, as the first of the progressive plaques [8, 9]. Lipid pools rich in proteoglycans (hyaluronan and versican) located near the medial wall, in areas that generally lack smooth muscle cells, define this lesion type. The luminal surface, however, is mostly rich in smooth muscle cells and often accompanied by infiltrating macrophage foam cells [10]. The precise origin of the "lipid pool" is debatable, although studies suggest that a loss of smooth muscle cells promoted by apoptosis may be involved as basement membranes remnants can be identified by periodic acid Schiff (PAS) staining. Another characteristic of these lesions is microcalcification, which is prominently seen with anionic stains such as the von Kossa's stain [9].
- The first of the advanced lesions are considered fibroatheromas (AHA Type IV), which are characterized by an acellular necrotic core, accumulated cellular debris and cholesterol monohydrate, and a lack of extracellular matrix [5, 8]. During the evolution towards a *fibroatheromatous*

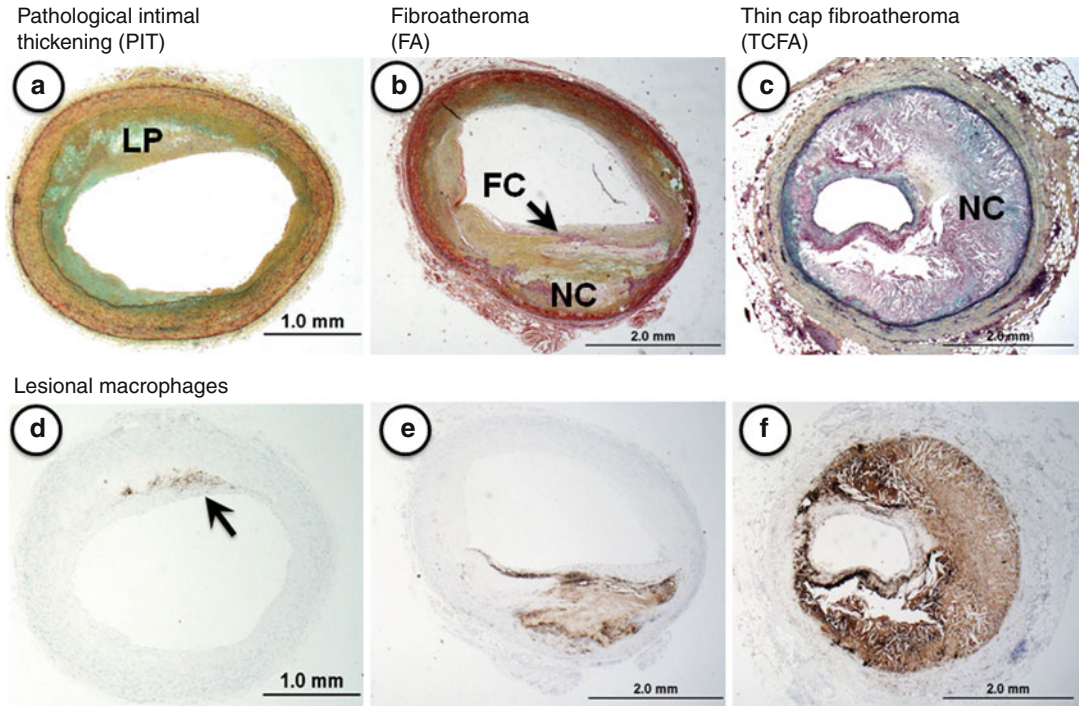


**Fig. 1.2** (**a**–**f**) Lesion morphologies consistent with progressive atherosclerosis: (**a**–**c**) Movat pentachrome staining; (**d**–**f**) CD68 immunostaining = macrophages). (**a**) Pathologic intimal thickening (*PIT*) is characterized by a non-flow limiting smooth muscle cell-rich lesion with an acellular lipid pool (*LP*) containing proteoglycan. (**b**) Fibroatheroma (*FA*) represents a lesions with a relatively thick fibrous cap (*FC*) overlying an area of necrosis or necrotic core (*NC*). These lesions are also generally non-flow limiting. (**c**) Thin-cap fibroatheroma (*TCFA*), shows a relatively large necrotic core with a thin fibrous cap typically infiltrated by macrophages and T-lymphocytes. The TCFA or "vulnerable plaque" is a know precursor to rupture. (**d**–**f**) These show the varying distribution of macrophages in progressive plaques. Note in (**d**) (*PIT*) the macrophages (*arrow*) are located near the luminal surface outside the area of the lipid pool, which is a distinguishing feature of this plaque

lesion, an overlying layer of fibrous tissue (fibrous cap) becomes identifiably distinct from the circumscribed area of necrotic core. The fibrous cap has a critical role in harboring the contents of the necrotic core, and its integrity is one of the defining influences on plaque stability (AHA Type V) [5]. The development of the necrotic core is believed to originate from apoptotic macrophages.

- The extent of fibrous cap thinning along with underlying necrotic core defines the thin-cap fibroatheromas (vulnerable plaque) [11, 12] while more complicated plaques are represented by surface defects, and/or hematoma-hemorrhage, and/or thrombosis (AHA Type VI) [5, 8]. By histology, thin cap fibroatheromas are considered high-risk plaques with fibrous caps of thickness less than 65 μm, which are typically heavily infiltrated by macrophages and T-cells [13]. This measure of fibrous cap thickness is derived primarily from histologic sections of plaque ruptures where cap thickness at rupture sites was found to measure 23 ± 19 μm with a 95 % confidence interval of 64 μm [13]. Lesions identified as thin-cap fibroatheromas are considered precursors to rupture since they retain most features of rupture except that the fibrous cap is intact without a superimposed luminal thrombus.
- The complications of hemorrhage, calcification, ulceration, and thrombosis in late stages of atherosclerosis are poorly understood. As recent as twenty-years-ago, the belief remained that acute coronary thrombosis was the sole cause