Arteriosclerosis
Rethinking the Current Classification

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Arteriosclerosis is literally the hardening of an artery. Standard textbooks of pathology and numerous other resources consistently list 3 lesions under the term arteriosclerosis: (1) atherosclerosis, (2) Mönckeberg medial calcific sclerosis, and (3) arteriolosclerosis. These lesions generally share 3 features: (1) they result in stiffening of arterial vessels; (2) they cause thickening of the arterial wall; and (3) in the past, they have been considered “degenerative” diseases. Herein we review the history of arteriosclerosis nomenclature, the current classification of arteriosclerosis, and the shortcomings of this classification. Finally, we review the subtypes of arteriosclerosis with emphasis on how future classification could more accurately and comprehensively categorize these lesions. This discussion includes examples of lesions that could qualify as arteriosclerosis yet are not currently classified as such. We exclude consideration of vasculitides, malformations, vascular dysplasia, connective tissue disorders, and neoplasms involving arterial vessels; the nomenclature of these lesions is already sufficiently complex and confusing.

HISTORY OF THE TERMINOLOGY AND CLASSIFICATION OF ARTERIOSCLEROSIS

The name arteriosclerosis is a term of Greek origin meaning “hardening of the arteries.” Though arteriosclerosis is a phenomenon believed to be prevalent since ancient Egypt, it only began to catch the attention of investigators in the latter half of the last millennium. In 1575, Fallopius writes of “a degeneration of arteries into bone.” These “ossified arteries” were commonly noted by anatomists of that period. Johann Friedrich Crell, in 1740, elucidated the phenomenon by asserting that the coronary artery hardenings were, in fact, not bony, but derived from pus. Fifteen years later, von Haller was first to identify such a lesion as an “atheroma,” a term used in Greek literature to describe a space filled with gruel-like matter. The first use of the term arteriosclerosis, however, can be attributed to Jean Frédéric Martin Lobstein in his critical analysis of the composition of calcified arterial lesions.

By the 20th century, the word arteriosclerosis described a disease state of multiple known etiologies. George Johnson can be awarded the distinction of being first to describe noncalcified, nonatheromatous stiffening of small vessels in his review of Bright disease, published in 1868. His contemporaries, Gull and Sutton, introduced the term “arterio-capillary fibrosis” to characterize this phenomenon, which would soon thereafter be referred to as arteriolosclerosis.

In 1903, J. G. Mönckeberg published a discussion of an arterial lesion he asserted was distinct from the forms of arteriosclerosis mentioned in the previous paragraphs. His name has since been associated with medial calcification, though, it is not clear whether the condition modern pathologists call Mönckeberg calcific medial sclerosis is the same pathology he described. Around the same time, Felix Marchand believed arteriosclerosis to be an inadequately general description of a disease that had now become the focus of much attention. He presented the term “atherosclerosis,” one he believed was more descriptive of...
the lesions of interest. Oskar Klotz\(^\text{12}\) was quick to point out that, although more specific, Marchand’s designation was not applicable to all arteriosclerotic lesions, like those described by Mönckeberg, in which no true atheroma is present.

In January of 1954, the *American Journal of Clinical Pathology* published a letter to the editor, written by S. M. Rabson,\(^\text{3}\) entitled, “Arteriosclerosis: Definitions.” In it, Rabson alludes to an article he had recently read featuring “arteriosclerosis” in its title but nowhere in its text. This prompted Rabson to send letters to various heads of university pathology departments, inquiring as to the meaning of words such as arteriosclerosis and atherosclerosis. The results of his survey were definitions that lacked specificity, uniformity, and consistency, a situation that we feel continues to this day. In his letter, a frustrated Rabson suggests that arteriosclerosis be a generic label used to describe any of the arterial pathologies we have discussed previously. The term atherosclerosis, he asserts, can reasonably be defined as “arteriosclerosis with atheromatosis,” and its use should be restricted to that specific condition. This definition, provided by Rabson, has persevered and remains the definition pathologists operate with today.

### CURRENT CLASSIFICATION

It appears that Rabson’s brief editorial became the foundation of the classification of arteriosclerosis that is used today. Currently, arteriosclerosis is classified into 3 lesions: (1) atherosclerosis, (2) Mönckeberg medial calcific sclerosis, and (3) arteriolosclerosis.

Atherosclerosis is a disease of elastic and large muscular arteries in which the atheroma is the characteristic lesion. The lesions of atherosclerosis enlarge the arterial intima with variable amounts and types of lipids, connective tissues, inflammatory cells, and a variety of extracellular components including matrix proteins and enzymes and calcium deposits.\(^\text{6,13,14}\) As atherosclerosis is the number one killer in industrialized countries, this lesion has been studied extensively, with great progress in understanding its pathogenesis, risk factors, natural history, treatment, and prevention. There are existing subclassifications of atherosclerosis, including one adopted by the American Heart Association.\(^\text{15}\) Although this classification is not without shortcomings,\(^\text{14}\) it has been generally accepted, so the subcategories of atherosclerosis are not discussed in this article.

Mönckeberg medial calcific sclerosis, as its name implies, is a calcification process that affects the media of large and medium-sized arteries. It is said to be a disease rarely seen in patients younger than 50 years. According to our German translators, Mönckeberg’s calcific lesions involve only the tunica media of arteries, without any compromise of the arterial lumen.\(^\text{16}\) However, Mönckeberg sclerosis and atherosclerosis may coexist.

Arteriolosclerosis, as its name implies, is a lesion of arterioles, small arterial vessels with 1 or 2 layers of smooth muscle cells. Arteriolosclerosis affects arterioles throughout the body and is most typically associated with hypertension and diabetes mellitus. There are 2 undoubtedly related, yet histologically distinct, subtypes of arteriolosclerosis: the hyperplastic type and the hyaline type.\(^\text{17}\)

### PROBLEMS WITH THE CURRENT CLASSIFICATION

There are 3 major problems with the current classification: (1) it has an inconsistent naming convention, (2) it fails to use terms that accurately describe the lesions, and (3) major sclerotic arterial lesions are absent from the classification. Another problem is that although the terms arteriosclerosis and atherosclerosis describe different lesions, these terms are used interchangeably. This inappropriate use of these terms has been pointed out by Aschoff\(^\text{18}\) almost 100 years ago, Rabson\(^\text{3}\) more than 60 years ago, and by others more recently.\(^\text{6}\)

The first problem of inconsistent naming is evident by the fact that the first 2 types of arteriosclerosis, atherosclerosis and Mönckeberg medial sclerosis, are defined by their gross and histopathologic features. On the other hand, arteriolosclerosis is defined by the size of the involved vessel. The term arteriolosclerosis does not describe any pathologic characteristics. Clearly, a classification should be consistent. That is, the classes should have similar descriptors, either based on the pathology, or based on the anatomic site of the lesion, but not one or the other. ‘‘Arteriolo’’ is not a pathologic lesion but rather a prefix that qualifies the lesion to very small arteries. Only the terms for the subtypes of arteriolosclerosis, hyaline arteriosclerosis and hyperplastic arteriolosclerosis, elucidate the histopathology.

The second problem is that the current system of naming does not describe these lesions accurately. Even the term arteriosclerosis is perhaps a misnomer; many quintessential arteriosclerotic lesions are not in fact hardened arteries. In recent years, researchers have paid much attention to so-called vulnerable atherosclerotic plaques, or “thin fibrous cap atheromas”—plaques in which a thin sheath of fibrous tissue envelopes a large lipid core.\(^\text{19}\) Indeed, these are often soft plaques yet we describe them as sclerotic or hardened.

Furthermore, the term Mönckeberg medial sclerosis is most likely being used incorrectly. The lesion that is generally regarded as Mönckeberg medial sclerosis, ironically, may not be the lesion that Mönckeberg himself described. On review of the medical literature, we found 25 articles or texts that described “Mönckeberg medial sclerosis.” In 10 of these publications the authors state that Mönckeberg sclerosis involves the internal elastic lamina (IEL); in the other 15 publications the authors stated that the IEL is free of calcification.\(^\text{10}\) In our own experience, and formal review of 14 specimens with calcification of the arterial media, all cases also had calcification of the IEL.

Often there were portions of the artery with only IEL calcification.\(^\text{20}\) Thus, the weight of evidence indicates that the lesion inaptly regarded as medial sclerosis actually involves the IEL—regarded by anatomy textbooks as intima\(^\text{21–23}\)—and may or may not involve the media.

The third, and perhaps the most important, problem is that there are important arterial lesions of which everyone is aware that are not yet part of the current classification. These include transplant arteriopathy, restenosis lesions after balloon angioplasty and stenting, intimal nonatherosclerotic proliferative lesions in arterial vessels larger than arterioles, and a variety of disorders associated with vascular calcification, not generally regarded as Mönckeberg sclerosis.

Transplant arteriopathy, generally a nonatherosclerotic hyperplastic fibromuscular intimal proliferation, occurs in...
virtually all types of solid organ transplants. Transplant arteriopathy affects large and small muscular arteries and veins as well. Early on, there is inflammation in the vessel that can be mild or marked which may involve 1 or more of the 3 layers. Usually, the intima is affected more than the media or adventitia, but sometimes even a transmural, necrotizing arteritis may occur. Following the inflammatory stage is the typical intimal fibromuscular proliferation. With time, the lesions become less cellular and more fibrotic. Calcification, thrombosis, and atheroma formation can also occur in the setting of transplant arteriopathy. In the heart, where this lesion is most damaging, transplant coronary artery disease affects large and small epicardial coronary arteries and intramyocardial arteries.

Another now common iatrogenic form of intimal hyperplasia is that associated with restenosis after balloon angioplasty or after intravascular stent placement. The intimal proliferation in restenosis lesions is histologically the same as in transplant arteriopathy and the hyperplastic form of arteriolosclerosis.

There are a number of other situations in which arteries, not arterioles, show lesions histologically similar to those seen in the hyperplastic type of arteriolosclerosis lesions. One commonly encountered site for such lesions is the temporal artery. In elderly patients in whom biopsy is negative for temporal arteritis, these intimal lesions are often observed. Indeed, in the American Heart Association classification of arteriosclerosis, the atheroma-prone lesion is not the fatty streak but rather a region of intimal fibromuscular hyperplasia, referred to as “adaptive intimal thickening.” Identical lesions may be seen throughout the body as a nonspecific finding in muscular arteries.

Although the term intimal hyperplasia is often used to describe intimal thickening with smooth muscle cells, collagen, and other components present, we recognize that this phrase may not be completely accurate. Because smooth muscle cells in the intima may have migrated from the media or adventitia, or have been deposited from circulating progenitor cells, the process in the intima is not simply hyperplasia. Furthermore, there are a variety of other terms used synonymously to describe intimal thickening, such as neointima, fibromuscular hyperplasia, adaptive intimal thickening, hypertrophy, and fibroplasia, just to name some. Whether or not these are appropriate for specific lesions, or truly synonymous, requires additional study.

In addition to what Mönckeberg described, there are a number of other patterns of arterial calcification. We recently reported calcification limited to the IEL observed in the coronary arteries of human immunodeficiency virus (HIV)–positive patients and HIV-negative elderly patients with a variety of chronic diseases. These patients had normal renal function. In patients who do have renal dysfunction, alterations in calcium metabolism may cause widespread tissue calcification that affects the arterial bed, so-called vascular tachyphylaxis. Renal failure can also result in more extensive calcification within atherosclerotic plaques and/or extensive medial calcification that affects arteries throughout the body. In patients with secondary hyperparathyroidism, x-rays of the hands may reveal such calcification in digital arteries. In diabetic patients with severe peripheral vascular disease, arteries in amputated limbs frequently show heavily calcified atherosclerotic plaques and marked medial calcification. Importantly, electron beam computed tomography of coronary arteries in patients with chronic renal disease yields higher calcium scores than in individuals with normal renal function. Whether this calcification is in the atherosclerotic lesions or the arterial media has not been addressed.
Figure 2. A and B, Atherosclerosis. A, Characteristic eccentric lesion with large lipid-rich (necrotic) core covered by a fibrous cap (F) (hematoxylin-eosin, original magnification $\times 2$). B, Oil red O stain showing lipid (L-red) within the lipid-rich core (original magnification $\times 40$). Smaller darker red dots are lipid-laden macrophages. C, So-called Mönckeberg medial calcific sclerosis. Note that although there is prominent medial calcification the internal elastic lamina is also involved (arrow) (hematoxylin-eosin, original magnification $\times 40$). D through F, Primary arterial calcification. D, Early lesion with interrupted linear calcification limited to the internal elastic lamina (hematoxylin-eosin, original magnification $\times 100$). E, von Kossa stain of early lesion with interrupted linear calcification limited to the internal elastic lamina (original magnification $\times 100$). F, Linear and nodular calcification of the internal elastic lamina (arrows) (hematoxylin-eosin, original magnification $\times 20$).
Figure 3. A through D, Fibromuscular intimal thickening. A, “Adaptive intimal thickening” in proximal coronary artery (trichrome, original magnification ×40). B, Transplant coronary artery disease (trichrome, original magnification ×40). C, Intimal hyperplasia in temporal artery (hematoxylin-eosin, original magnification ×40). D, Arteriolonephrosclerosis, hyperplastic type (hematoxylin-eosin, original magnification ×200). E and F, Hyalinosis (hematoxylin-eosin, original magnification ×200 [E] and periodic acid–Schiff, original magnification ×200 [F]).

CATEGORIES OF ARTERIOSCLEROSIS

Figure 1 shows the subtypes of arteriosclerosis organized into what we believe are the various categories based on the major light-microscopic pathology of the lesions. In the following we describe each subtype in greater detail and explain, in our opinion, how each could be represented in future classifications of arteriosclerosis.

Atherosclerosis

Atherosclerosis (Figure 2, A and B) is clearly the most important arteriopathy. Although the suffix “sclerosis” is
Figure 4. A and B, Vascular amyloidosis causing stenosis of intramyocardial arteries from a patient who died suddenly (hematoxylin-eosin, original magnification ×100 [A] and Congo red, original magnification ×100 [B]). C and D, Coronary artery of a patient with oxalosis; crystal deposits are subtle by routine light microscopy but prominent under polarized light (hematoxylin-eosin, original magnifications ×100 [C and D]). E, Oxalate was also present within a calcified (C) atherosclerotic plaque (hematoxylin-eosin, original magnification ×40).

Derived from the Greek word meaning hardening, atherosclerotic vessels may not be harder than normal and, indeed, may even be softer. One might even consider atherosclerosis an oxymoron. Although sclerosis denotes hardening, “athero” literally means gruel-like. Atherosclerosis is therefore literally, and rather unintuitively, defined as arteries hardened by a thin chunky liquid. Alternate terms for some of the lesions might include atheromatous arteriomalacia or atheromatous arteriopathy. However, historically these are referred to as sclerotic lesions, not hard lesions, as they have become semantically distinct terms. In addition, it is quite common for the definition of a term to semantically deviate from its Greek derivation. Indeed, though hippocampus literally means sea horse,
we accept that this historical nomenclature is not to be taken literally. Furthermore, the word sclerosis is commonly applied in other pathologies in which hardening is not the characteristic change, such as multiple sclerosis and hippocampal sclerosis. Therefore, it is not difficult to accept atherosclerosis as a worthy subtype of arteriosclerosis.

Mönckeberg Medial Calciﬁc Sclerosis

Because the term Mönckeberg medial calciﬁc sclerosis (Figure 2, C) is probably only partially accurate and because there are other forms of arterial calciﬁcation, we feel this and other nonatherosclerotic forms of arterial calciﬁcation are better described as “primary arterial calciﬁcation.” We have observed primary arterial calciﬁcation in 3 patterns.

Calcification limited to the IEL is a common phenomenon in temporal arteries. Internal elastic lamina calciﬁcation occurs infrequently in coronary arteries (Figure 2, D through F). We described 19 cases of coronary artery IEL calciﬁcation; 10 patients were HIV-positive patients and 9 HIV-negative patients had a variety of chronic illnesses. Sometimes, calciﬁcation encroached on adjacent intimal or medial tissue and was associated with mild ﬁbrosis. There was frequent disruption of the IEL but no inﬂammation. von Kossa, alizarin red S, and trichrome/elastin stains conﬁrmed the ﬁndings. Patients with IEL calciﬁcation often had complex medical histories but did not suffer from chronic renal failure or other conditions known to cause calcium dysregulation. The pathogenesis and clinical signiﬁcance of this ﬁnding are unknown. However, this mysterious calciﬁcation could lead to arterial stiffening and increased pulse pressure and could be mistaken for intimal calciﬁcation on coronary imaging. IEL calciﬁcation may result from premature aging due to HIV disease and chronic illness or from metabolic disorders in HIV-positive patients. Because IEL calciﬁcation is not part of any classiﬁcation, IEL calciﬁcation is probably underreported.

Although Mönckeberg medial calciﬁc sclerosis is not entirely medial and probably begins in the IEL, it is not our intention to rob Mönckeberg of his namesake. Given the historical context, we feel Mönckeberg will continue to be associated with calciﬁcation limited to the arterial media. Incidentally, however, this pattern of calciﬁcation may be exceedingly rare or simply may not occur at all. We encourage others to conﬁrm our observations suggesting that medial calciﬁcation is virtually always associated with calciﬁcation of the IEL.

The third pattern of primary arterial calciﬁcation would be a combination of the ﬁrst two; that is, calciﬁcation of both the IEL and the media. We believe this will eventually prove to be the primary pattern of calciﬁcation in which the arterial media is involved.

Arteriolosclerosis

We feel the third category, arteriolosclerosis, which distinguishes small artery sclerosis from large artery sclerosis, is an unnecessary distinction. The subtype “ﬁbromuscular intimal thickening” (Figure 3, A through D) would include the hyperplastic form of arteriolosclerosis but would similarly include ﬁbromuscular hyperplasia in arteries, as seen in transplanted vasculopathy, restenosis lesions after balloon angioplasty or stenting, and nonspeciﬁc intimal thickening as occurs in temporal arteries with aging. Although hyalinosis typically occurs in arterioles, similar changes can be seen in arteries. Thus, simply describing these lesions as intimal hyalinosis would include such changes in arteries as well as arterioles (Figure 3, E and F).

Finally, there are those miscellaneous entities that share features of the lesions discussed so far in that they cause thickening and stiffening of arteries. Two recent examples we have encountered that are not included in existing categories of vascular diseases are amyloidosis, which can involve arteries and arterioles, and vascular oxalosis (Figure 4, A through E).

Vascular involvement by amyloid deposits is a well-known phenomenon. Amyloid deposits in large and small arteries can cause ischemia and even sudden death when either the epicardial or intramyocardial coronary arteries are involved.

Oxalosis is a relatively rare metabolic abnormality that may be hereditary or acquired. Oxalate deposits most often occur in the media of elastic and muscular arteries in patients with chronic renal failure. However, we recently reported, for the ﬁrst time, intimal deposition of oxalates in atherosclerotic plaques, so-called atherosclerotic oxalosis. In a review of coronary arteries from 80 patients, we found 4 cases in which there were prominent oxalate deposits within the atherosclerotic plaques in coronary arteries. Oxalate deposits were also present in the media of arteries, the thyroid gland, and other organs, but not the kidneys, and the patients surprisingly did not have renal failure.

Another group of disorders that are associated with vascular lesions that could qualify as arteriosclerosis are systemic genetic disorders such as the mucopolysaccharidoses (Hunter and Hurler syndromes) and Alagille syndrome. These might also be included in a miscellaneous category along with other vascular lesions.

As mentioned, there are other categories of arterial diseases: vasculitides, neoplasms, malformations, angiodysplasias, and inheritable disorders of connective tissue. Whether or not these should be incorporated into an all-inclusive classiﬁcation is beyond the scope of our editorial.

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