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Perspective

Arteriosclerosis: facts and fancy

Michael C. Fishbein *,[1], Gregory A. Fishbein

David Geffen School of Medicine at UCLA, Department of Pathology and Laboratory Medicine, Los Angeles, CA 90095

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ABSTRACT

Arterial vascular diseases comprise the leading cause of death in the industrialized world. Every physician learns about the pathology of these diseases in medical school. All pathologists evaluate arterial disease in surgical pathology and/or autopsy specimens. All clinicians encounter patients with clinical manifestations of these diseases. With such a common and clinically-important group of entities one would think there would be a general understanding of the "known" information that exists. That is, physicians and scientists should be able to separate what is fact and what is fancy. This review article is intended to generate thought in this regard.

1. Introduction

Arterial diseases, namely atherosclerosis and arteriolosclerosis, are arguably the most lethal diseases in industrialized countries leading to sudden death, myocardial infarction, heart failure, stroke, kidney failure, and ischemia of limbs and major internal organs. In spite of the lesions' importance, there has been little interest in terms, classification, and in our opinion, the true nature of some of the entities under the rubric of "arteriosclerosis".

The purpose of this review is to re-examine the topic of arteriosclerosis in a non-conventional, critical, somewhat tongue-in-cheek, and perhaps, controversial manner.

Fact or Fancy #1: The lesions of arteriosclerosis are less than 300 years old.

Answer #1: Fancy.

Discussion: The *terms* used to describe the lesions of arteriosclerosis are less than 300 years old. In 1755 Van Haller used the Greek term "atheroma" to describe a space filled with gruel-like material [1]. In 1833, Frenchman Jean Frederic Martin Lobstein first used the terms "arteriosclerosis" to describe calcified arterial lesions [2]. In 1852, Johnson described the lesions of "arteriolosclerosis" a thickening of arterioles of the kidney [3]. In 1903, Mönckeberg described "medial calcific sclerosis" [4]. In 1904 Marchand coined the term atherosclerosis [5]. Hence, the terms we use today are not very old. On the other hand, both atherosclerosis and Mönckeberg's medial calcific sclerosis are described by Sir Marc Armand Ruffer in his examination of Egyptian mummies [6]. So while the terminology is less than 300 years old, the lesions are thousands of years old. Hence the answer to query #1 is: Fancy.

Fact or Fancy #2: The current classification of arteriosclerosis is based on a consensus document by a major cardiovascular or pathology organization.

Answer #2: Fancy.

Discussion: The current classification of arteriosclerosis, as defined in classic textbooks of pathology (e.g., Robbins [7]), contains three lesions: atherosclerosis, Mönckeberg's medial calcific sclerosis, and arteriolosclerosis (Fig. 1). Atherosclerosis is a disease of elastic and large muscular arteries in which the atheroma is the characteristic lesion. Mönckeberg's is a calcification process that, according to Mönckeberg [4] involves only the tunica media. Mönckeberg's may be idiopathic or associated with diabetes mellitus and/or renal failure. Arteriolosclerosis is a thickening of the wall of very small arteries, those with one or two layers of smooth muscle cells, by intimal fibromuscular tissue or "hyaline" deposition, typically associated with hypertension or diabetes. While in recent years efforts have been made to establish a consensus classification for atherosclerosis [8–11], as best we can tell, the current classification of *arteriosclerosis* comes from a one page editorial in the *American Journal of Clinical Pathology*, 24:472–473, 1954, *Arteriosclerosis Definitions*, by S. M. Rabson, who wrote:

> "May not arteriosclerosis be employed as the generic term covering the condition seen in the aorta and the coronary artery (atherosclerosis), in medial calcification of elastic artery (Mönckeberg's sclerosis), in hyaline thickening of the arteriole (arteriolosclerosis), to name only the most prominent disturbances". As this appears to be the basis of the current

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* Corresponding author at: David Geffen School of Medicine at UCLA, Department of Pathology and Laboratory Medicine, 10833 Le Conte Avenue, CHS 13-145, Los Angeles, CA 90095, USA.

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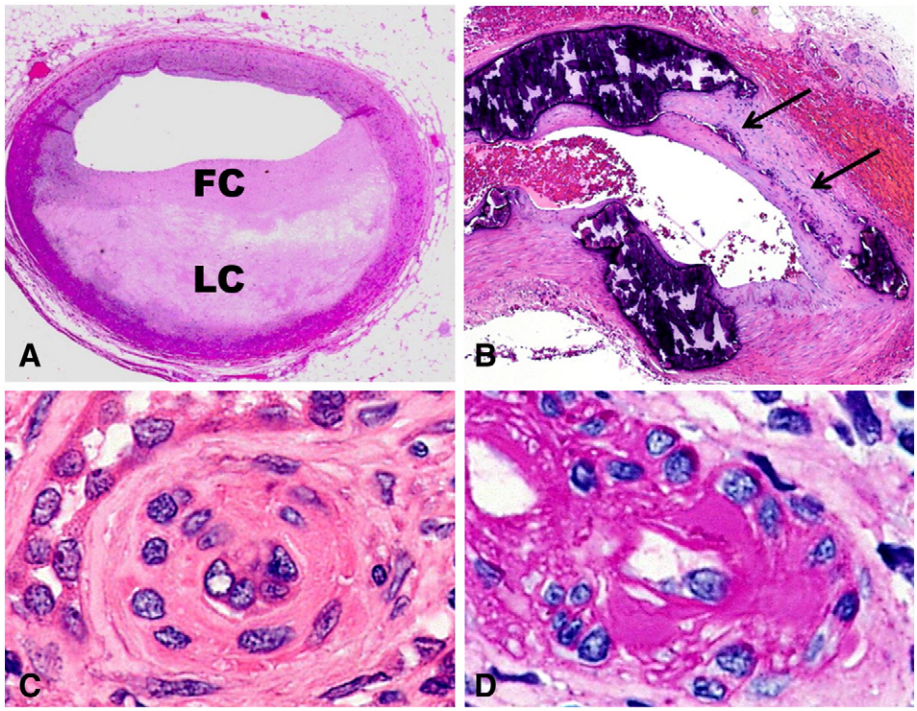

Fig. 1. Lesions recognized in current classification of arteriosclerosis: (A) atherosclerosis with lipid core (LC) and fibrous cap (FC) (H&E, ×12.5); (B) Mönckeberg's "medial" calcific sclerosis. Note involvement of internal elastic lamina (arrow) (H&E, ×20); (C) arteriolosclerosis, hyperplastic type, AKA fibromuscular hyperplasia (H&E, ×200); and D) arteriolosclerosis, hyaline type, AKA hyalinosis (H&E, ×100).

classification of arteriosclerosis, the classification is not based on a consensus statement by any cardiovascular or pathology organization. Hence the answer to query #2: Fancy.

Fact or Fancy #3: Mönckeberg's medial calcific sclerosis is a disease of the media.

Answer #3: Fancy.

Discussion: This appears to be a silly question, akin to "Who is buried in Grant's Tomb?" However, if one examines the literature on this topic, one finds that half the references say Mönckeberg's only affects the media, while the other half of the references state that the intima is also involved. Strangely, in the 1961 edition of Anderson's Textbook of Pathology [12], it is stated that in Mönckeberg's, "calcium is deposited in the form of plaques in the mid-portion of the media…" while in the 1971 edition of the same textbook [13] it states that Mönckeberg's consists of calcification "involving the media and internal elastic lamina of muscular arteries of the head and neck and extremities". In Mönckeberg's original article there are no photomicrographs or drawings, but the text states that only the media is involved. In our own study of arteries with lesions diagnosed as Mönckeberg's medial sclerosis, 100% of cases had involvement of the internal elastic lamina [14]. In fact, in less severe cases, it appears that the lesion actually begins in the internal elastic lamina and then grows and extends into the media. Hence, the lesion we call Mönckeberg's medial sclerosis is not purely a medial lesion, and apparently is not the lesion described by Mönckeberg. Therefore the answer to query #3 is: Fancy.

Fact or Fancy #4: The third category, arteriolosclerosis, defines a specific pathogenic entity affecting small arteries.

Answer #4: Fancy.

Discussion: The term arteriolosclerosis actually does not define a lesion at all. It is a generic term meaning "hardening of small arteries". In fact, the term encompasses two distinct lesions: 1) a fibromuscular proliferation of the intima, the "hyperplastic type", and 2) a deposition of amorphous material in the arteriolar wall, the "hyaline type". Unlike the two terms atherosclerosis and Mönckeberg's medial sclerosis that define pathologic patterns, the term arteriolosclerosis does not—a problem in the classification. Hence the answer to query #4: Fancy.

Fact or Fancy #5: As was true when Rabson wrote his editorial in 1954 [15], the current classification of arteriosclerosis names the most prominent disturbances.

Answer #5: Fancy.

Discussion: There are a number of common lesions, both natural and iatrogenic, that cause non-atherosclerotic, primarily fibromuscular proliferation in the intima of muscular arteries larger than arterioles (Fig. 2). The natural lesions include nonspecific intimal thickening, frequently seen in temporal artery biopsies and other sites. Important iatrogenic lesions include transplant-related arteriopathy and "restenosis lesions" following balloon and/or stent angioplasty.

Fact or Fancy #6: While imperfect, the current classification of arteriosclerosis does include all types of arterial calcification.

Answer #6: Fancy.

Discussion: While Mönckeberg's sclerosis and atherosclerosis are arterial lesions with the greatest degree of calcification, another pattern exists (Fig. 3): calcification limited to the internal elastic lamina is observed and described in temporal arteries, for example. We observed similar calcification in coronary arteries of HIV positive and control patients in a study of HIV-related cardiovascular disease, using specimens from our AIDS tissue bank [16]. To our surprise, we could find no prior reference to this pattern in coronary arteries.

Also surprising was the fact that this calcification was not associated with renal failure, diabetes mellitus, or disorders associated with abnormal calcium levels. What about calciphylaxis? Calciphylaxis is undoubtedly a process that causes hardening of the arteries. Nevertheless, classic textbooks of pathology do not include calciphylaxis in the classification of arteriosclerosis. Based on the fact that calciphylaxis is a form of vascular calcification, and calciphylaxis is not covered in the current classification, the answer to query #6: Fancy.

Since there are entities, such as those heretofore described, that cause hardening of the arteries but are not considered arteriosclerosis, we urge consideration of a new, more comprehensive, accurate