Arteriosclerosis: facts and fancy

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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 arteriosclerosis [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 arteriosclerosis [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
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 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
Classification. We previously published a suggested start for efforts in that direction [17] (Fig. 4).

Fact or Fancy #7: Clinically-significant atherosclerotic plaques originate as fatty streaks, then progress to fibrous plaques, and finally progress to the only clinically-significant plaques, the complicated plaque.

Answer #7: Fancy.

Discussion: While the standard teaching is that clinically-significant atherosclerotic plaques begin in fatty streaks, investigators have questioned this evolution[1]. Basically, all that fatty streaks and complicated plaques have in common is lipid. Racial groups that are born with more fatty streaks in the aorta have fewer complicated plaques. Fatty streaks in the aorta are most often posterior midline, while raised plaques are more often anterior and lateral. Fatty streaks are more common in the proximal aorta, while raised plaques are more common in the distal aorta. Mouths of intercostal arteries are usually free of fatty streaks, but raised plaques often develop at that site. Furthermore, the most important raised plaques, those that develop in coronary arteries, develop in regions of adaptive intimal thickening (AIT) (Fig. 5).

These are regions with intimal smooth muscle and extracellular matrix that demonstrate increased turnover of smooth muscle cells and endothelial cells, increased permeability, increased concentration of low density lipoproteins, and low shear stress and/or high wall tensile stress. So the progression and evaluation of clinically-significant atherosclerotic plaques may not involve the fatty streak. Hence the answer to query #7: Fancy.

Fact or Fancy #8: Atherosclerosis is a primary inflammatory disease.

Answer #8: Fancy.

Discussion: It is difficult to pick up a contemporary article on atherosclerosis that does not begin with the statement that “atherosclerosis is an inflammatory disease”. There is no question that inflammation plays a role in the progression and complications of atherosclerosis. Atherosclerosis has also been thought to be an infectious disease, a degenerative disease, and even a primary proliferative disease. However, it is also quite clear and has been understood for over 100 years that the first event in atherogenesis is low density lipoproteins entering the arterial wall. It is the presence of these lipoproteins that become oxidized that initiates the inflammation seen in atherosclerotic plaques. Furthermore, major studies of atherosclerosis, such as the MR FIT study, always show a relationship between the frequency of coronary events and cholesterol levels. Populations that have low blood cholesterol levels have fewer coronary events.

Hence atherosclerosis is a primary disease of lipids, not inflammation, so the answer to query #8: Fancy.

Fact of Fancy #9: The concept that inflammation plays a role in the progression of atherosclerosis is a new idea.

Answer #9: Fancy.

Discussion: Recent research work has identified molecular and cellular pathways of inflammation that participate in the process of atherosclerosis. While contemporary investigators continue to elucidate the details of the inflammatory response in atherosclerotic disease, past investigators have noted the inflammation and its importance in the progression and complications of atherosclerosis. In 1856 Rudolf Virchow introduced the term “endarteritis chronica” to describe atherosclerosis, ascribing atheroma formation to chronic irritation—an inflammatory process. In 1928, in a paper entitled “An inflammatory basis for coronary thrombosis”, A.N. Boyd stated that “…an atherosclerotic plaque may suddenly undergo an acute degeneration associated with inflammation and that thrombosis may be the result.” Hence the answer to query #9: Fancy.

Fact or Fancy #10: Current known risk factors can reliably identify individuals at increased risk of a coronary event.

Answer #10: Fancy.

Discussion: Table 1 lists generally accepted risk factors for coronary events, but we all have seen cases where patients have no risk factors, yet have severe atherosclerosis, while other patients have multiple risk factors, yet have no clinically significant disease. Epidemiologists tell us that risk factors account for about 50% of the risk of an event. Furthermore, new risk factors are being identified all the time (Table 2). Exposure to particulate matter in the atmosphere (i.e. air pollution) has been associated with an increased risk of coronary event. This observation adds new meaning to the phrase “living in a safe neighborhood.” More recently and more irritating is the finding that it is not only our metabolism, but also the way our intestinal microbiota metabolize our food that promotes atherosclerosis. Apparently our intestinal bacteria metabolize certain foods we eat, releasing pro-atherogenic compounds in our vascular system. So it is not our metabolism, but that of our intestinal bacteria that may determine whether or not atherosclerosis develops. To add injury to insult, now, genetically-determined short stature has been shown to be a risk factor for coronary artery disease. Sometimes our genes just conspire against us.

The above are examples of novel discoveries that are identifying new risk factors. Hence, the answer to query #10: Fancy.
Fact or Fancy #11: Currently, there is a comprehensive understanding about the “vulnerable” atherosclerotic plaque and why it ruptures. 
Answer #11: Fancy.
Discussion: There is a consensus regarding the definition of a vulnerable atherosclerotic plaque; however, there are major gaps in our knowledge about such plaques. Generally speaking, a vulnerable atherosclerotic plaque is one that is at high risk of rupture and/or one that is thrombosis prone. Once the plaque ruptures, the antithrombotic endothelium is injured and the pro-thrombotic contents of the plaque are exposed to the circulating blood promoting thrombosis at the site of intimal disruption. Histologically, the vulnerable plaque is an inflamed, thin-cap fibroatheroma with a large lipid core. It should be kept in mind that the association of this histologic pattern to plaque rupture is just that—an association. There is no established cause/effect relationship, in great part due to the lack of a reliable experimental model that mimics the human situation. Hence the answer to query #11: Fancy.
Fact or Fancy #12: The relationship between coronary artery plaque rupture and thrombosis is a relatively new discovery. 
Answer #12: Fancy.
Discussion: In a number of related papers in the 1980s and 1990s, Dr. Michael Davies “revived” the notion that plaque rupture leading to thrombosis was the predominant finding in patients who suffered sudden cardiac death or myocardial infarction due to atherosclerotic coronary artery disease [37]. Indeed, he reported acute changes in the “culprit” lesion in over 75% of such cases. To give credit where credit is due, we should acknowledge that a number of investigators before Davies tried to promote the same concept [30,38–49] (Table 3), but the concept never really caught on until Davies’ publication. Hence the answer to query #12 is: Fancy.
Fact or Fancy #13: A disproportionate number of plaque ruptures occur in the shoulder region of the plaque. 
Answer #13: Fancy.
Discussion: Much of the current investigation of vulnerable plaques involves study of the shoulder region of the plaque, the site believed to be most susceptible to rupture. What is the basis for this perception? Perhaps the most often cited work promoting this concept comes from a paper by Richardson, Davies, and Born in Lancet in 1989 [50]. The authors reported that of 67 plaques with an eccentric lipid pool, 42 (63%) had torn at the junction of the plaque cap with the adjacent normal intima, and 25 (37%) through the center of the cap. Thus it appears that 2/3 of plaque ruptures involve the shoulder. While that may be true, in cross-section, the plaques described would have one central region and two shoulders (Fig. 6). Therefore if plaque rupture were a random event in such plaques, 2/3 would involve the shoulder region and 1/3 the central region. Accordingly, if indeed there is
something special about the shoulder region, the data from this study do not really establish that the number of ruptures in the shoulder region is greater than were it a completely random process. Hence the answer to query #13: Fancy.

Fact or Fancy #14: “Non-stenotic lesions account for the majority of culprit ruptured plaques [51].”

Answer #14: Fancy.

Discussion: There has been the general notion that the smaller, non-occlusive plaque ruptures more frequently than large occlusive plaques, and that most coronary events are related to such smaller plaques. What is the basis for this concept? There have been a number of angiographic studies in patients who had coronary angiography months before, and immediately after, a coronary event [52–57]. According to the authors, before the coronary event, the culprit lesions were actually small non-occlusive plaques. If one actually looks at the data from these studies (Table 4), about 50% of the culprit lesions showed less than 50% diameter stenosis (equal to 75% cross-sectional area stenosis). These findings are different from pathologic studies of fatal myocardial coronary events [49,58–60] (Fig. 7). In these pathologic studies (Table 5), only 14% of plaque rupture with thrombosis occurred in arteries with less than 75% cross-sectional narrowing. The angiographic studies were questioned years ago (see Fishbein MC, Siegel RJ. How big are coronary atherosclerotic plaques that rupture? [61]). However, only recently, with the advent of novel, better imaging modalities, has the paradigm shifted. In the COURAGE trial [62], 2287 patients with stable coronary artery were randomized to either optimal medical therapy or percutaneous intervention and medical therapy. In patients randomized to medical therapy who had a coronary event, the majority of responsible lesions had greater than 50% diameter narrowing at the time of...
randomization. Very few events were due to progression of lesions that had less than 50% diameter narrowing [63].

A more recent study by Tuan et al. using OCT, IVUS, and angiography also found that most “vulnerable” thin-cap fibroatheromas were present in more, rather than less, stenotic regions. Fig. 6b demonstrates how a plaque rupture might appear to be occurring in a small plaque. If the rupture occurs at the shoulder of the plaque, which is likely not the region of maximum narrowing of the plaque, which, in the diagram, is more downstream. This phenomenon has been documented in angiographic studies [64].

Hence, the answer to query #14: Fancy. A major, perhaps the major question concerning plaque rupture is, “why does rupture occur when it does?” Unfortunately, we don’t have a good experimental model, and it is probably impossible to study this experimentally in man, so we have to rely on epidemiologic data.

So far the answer to all 14 questions so far, in our opinion, is Fancy. Fact or Fancy #15: Watching soccer causes plaque rupture.

Answer #15: (Believe it or not!) Fact

Discussion: Wilbert-Lampen et al. reviewed the number of coronary events in Germany during the World Cup Soccer Tournament in 2003, 2005, and 2006 [65]. The authors observed spikes in the number of acute myocardial infarction increased on the days of the Brazilian team’s matches during World Cup soccer in 1998, 2002, 2006, and 2010 [66]. Similarly, in England, admissions for acute myocardial infarction increased by 25% on June 30, 1998—the day England lost a World Cup soccer match to Argentina in a penalty shoot-out [67]. While there are undoubtedly cardiovascular benefits to playing competitive soccer, the data are clear—spectators are at increased risk. So indeed, the answer to query #15: Fact. Watching soccer causes plaque rupture.

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References

Fig. 7. (A–F) Examples of culprit coronary arteries from patients with sudden cardiac death. Note arteries narrowed by large atherosclerotic plaques with occlusive luminal thrombus (T) (all H&E, ×12.5).

Table 5

<table>
<thead>
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<th>Percent cross-sectional area narrowing</th>
<th>&lt;50 n (%)</th>
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<th>&gt;74 n (%)</th>
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<td>11 (25)</td>
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<td>Qiao [60]</td>
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<td>Totals</td>
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<td>56 (11)</td>
<td>418 (86)</td>
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Notes: Data adapted from original articles.

*75% cross-sectional narrowing equals 50% diameter narrowing.