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Coronary Artery Aneurysms: An Update

Department of Pathology, Faculty of Medicine of Ribeirão Preto, Ribeirão Preto, University of São Paulo, Brazil

1. Introduction

Coronary artery aneurysm (CAA) is a neglected topic in the pathology literature; most descriptions of CAAs have been limited to reports of single cases and some reviews. Because CAAs are usually found incidentally during cardiac examinations, most of the reported cases have been diagnosed by coronary angiography, intravascular ultrasound and, on rare occasions, during autopsy (Ramos et al., 2008). Although they are rare, CAAs can be potentially fatal if they are not managed in a judicious and timely manner.

The first description of a CAA has been attributed to Morgagni, an Italian anatomopathologist of the mid-18th century. However, the first CAA in a living patient was diagnosed by coronary angiography (Munkner et al., 1958). Since then, many studies have been conducted on the pathology of abnormal dilatations of the coronary arteries; however, attempts at defining and classifying these abnormalities still create problems for researchers and physicians who work in this area. The major problem is differentiating between aneurysms and ectasias. Currently, CAA is defined as a localized, irreversible dilatation of the blood vessel lumen that exceeds the diameter of the adjacent normal segment by more than 1.5-fold (Falsett & Carrol, 1978; Swaye et al. 1983; Syed & Lesch, 1997). In contrast, ectasia is used to describe a diffuse dilatation of coronary arteries that involves 50% or more of the length of the artery; this classification is made according to the appearance and number of vessels involved (Markis et al, 1976). Ectasia has been subcategorized based on the topographical extent in the major epicardial coronary arteries into the following 4 types: type I, diffuse ectasia of two or three arteries; type II, diffuse ectasia in one artery and localized in another; type III, diffuse ectasia of one artery only; and type IV, localized and segmental ectatic lesions (Markis et al., 1976). The existence of the last type causes confusion in separating aneurysms from ectasias; therefore, additional efforts to define specific anatomic substrates will help to standardize the reporting of this disease and minimize discrepancies in the literature regarding management.

On rare occasions, a CAA grows large enough to be called a giant CAA, for which a precise definition is still lacking. Some authors consider coronary aneurysms to be giants when the CAA is greater than 2 cm (Mora et al., 2011), whereas the Committee of the American Heart
Association has defined giant aneurysms as those greater than 8 mm. In the literature, most of the reported maximum diameters of giant CAAs in adults have varied from 5 to 16 cm. Recently, cases of right giant CAAs have been recorded in MEDLINE and selected English-language articles describing CAAs with diameters exceeding 5 cm over a 10-year period (1998-2008; Ramos et al., 2008). A male predilection (63%) and a mean age of 58 years were observed. The most frequent cause was atherosclerosis (37%), especially in older patients. The symptoms of the CAAs varied, and only four patients were asymptomatic. Surgical resection was the treatment of choice (74%), and most patients underwent coronary artery bypass grafting (59%) or coronary artery reconstruction (7%). The majority of the patients had an uneventful recovery. Only 7% (2/27) of the patients died from cardiac causes related to the CAA (Ramos et al., 2008).

2. Incidence and anatomic distribution

A wide variation exists in the incidence of CAA. This variation can be attributed to the conceptual differences in the definition of coronary aneurysms and ectasia. In the literature, the incidence of coronary artery disease has been predominantly in men with an average age of 63.5 years (Befeler et al., 1977; Daoud et al., 1983). In the order of frequency, the following are the most affected coronaries: right coronary artery (RCA; 40.4%), left anterior descending artery (32.3%), left circumflex artery (23.4%), and rarely, left main coronary artery (3.5%); (Syed & Lesh, 1997). Atherosclerotic or inflammatory coronary aneurysms are usually multiple and involve more than one coronary artery. In contrast, congenital, traumatic, or dissecting aneurysms are usually single. Although coronary aneurysms are seen at any age, those related to atherosclerosis usually appear later in life than those associated with a congenital or inflammatory nature (Daoud et al., 1983).

3. Classification

CAAs have been classified in different ways based on the composition of the vessel wall and the morphological structure (Table 1). Aneurysms are often classified by macroscopic shape and size, according to the transversal and longitudinal size. Saccular aneurysms are spherical and show a transverse diameter greater than the longitudinal diameter, whereas fusiform aneurysms are characterized by a gradual and progressive dilatation that involves the complete circumference of the artery and have a transverse diameter that is smaller than the longitudinal diameter (Williams & Stewart et al., 1994). Moreover, CAAs may be true or false (pseudoaneurysms) depending on the composition of the aneurysmal wall. True aneurysms contain all normal vascular layers, and the blood remains within the confines of the circulatory system. False, or pseudoaneurysms, are extravascular hematomas that communicate with the intravascular space. Normal vascular integrity is usually lost, resulting in the formation of thin-walled structures that lack normal arterial wall layers. Pseudoaneurysms typically occur after disruption of the external elastic membrane and frequently result from blunt chest trauma or catheter-based coronary interventions (Aqel et al., 2004). Furthermore, pseudoaneurysms usually affect only a portion of the artery wall and are more vulnerable to thrombosis and rupture (Williams & Stewart, 1994).
Coronary Artery Aneurysms: An Update

Classification of CAAs

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Categories</th>
<th>Luminal diameter of the aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shape</strong></td>
<td>Saccular</td>
<td>Maximum transverse diameter &gt; longitudinal dimension</td>
</tr>
<tr>
<td></td>
<td>Fusiform</td>
<td>Longitudinal dimension &gt; maximum transverse diameter</td>
</tr>
<tr>
<td><strong>Vascular wall integrity</strong></td>
<td>True aneurysm</td>
<td>All vascular layers present</td>
</tr>
<tr>
<td></td>
<td>Pseudoaneurysm</td>
<td>Loss of the vascular wall integrity</td>
</tr>
<tr>
<td><strong>Topographical extent</strong></td>
<td>Type I</td>
<td>Diffuse dilatation of two or three vessels</td>
</tr>
<tr>
<td></td>
<td>Type II</td>
<td>Diffuse dilatation in one vessel and localized in another</td>
</tr>
<tr>
<td></td>
<td>Type III</td>
<td>Diffuse dilatation of one vessel only</td>
</tr>
<tr>
<td></td>
<td>Type IV</td>
<td>Localized or segmental dilatation</td>
</tr>
</tbody>
</table>

Modified from Antoniadis et al., 2008; Díaz-Zamudio et al., 2009.

Table 1. Morphologic and topographical classification of aneurysms and ectasias observed in coronary arteries.

4. Epidemiology

The prevalence of coronary artery disease in angiographic series has been documented to vary between 0.2 and 10%, but these studies have included both aneurysmal coronary disease and ectasias (Antoniadis et al., 2008). Because each angiographic diagnosis is operator-dependent, inter-observer variability may be responsible for the prevalence of discrepancies in different cohorts. Therefore, the documented frequencies may not represent the actual prevalence of coronary aneurysms in the general population. Moreover, one should not forget that a selection bias exists in patients referred for diagnostic coronary angiography. Table 2 shows exclusively the CAA prevalence in the most recent epidemiologic studies.

Undoubtedly, important genetic and environmental influences affect incidence, and the CAA incidence has been shown to be lower in Asia than in North America and Europe. In contrast, a study of 302 patients with Kawasaki disease showed an incidence of coronary aneurysms of 10.3% in patients of Asian ethnicity compared with 6.9% in those of Caucasian ethnicity and 1.2% in those of African ethnicity (Porcella et al., 2005).

<table>
<thead>
<tr>
<th>Source</th>
<th>Diagnosis</th>
<th>Population</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falsetti &amp; Carrol, 1976</td>
<td>Angiography</td>
<td>742</td>
<td>1.5</td>
</tr>
<tr>
<td>Daoud et al., 1983</td>
<td>Autopsy</td>
<td>694</td>
<td>1.4</td>
</tr>
<tr>
<td>Tunick et al., 1990</td>
<td>Angiography</td>
<td>8,422</td>
<td>0.2</td>
</tr>
<tr>
<td>Wang et al., 1999</td>
<td>Angiography</td>
<td>10,120</td>
<td>0.1</td>
</tr>
<tr>
<td>Harikrishnan et al., 2000</td>
<td>Angiography</td>
<td>3,200</td>
<td>0.7</td>
</tr>
<tr>
<td>Groenke et al., 2005</td>
<td>Angiography</td>
<td>7,101</td>
<td>1.4</td>
</tr>
<tr>
<td>Rozenberg &amp; Nepomnyashchikh, 2005</td>
<td>Autopsy</td>
<td>1,000</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Table 2. Prevalence of coronary artery aneurysms in angiographic and autopsy studies.
5. Etiology

Coronary atherosclerosis and Kawasaki disease are the principal causes of CAAs. Atherosclerosis is the most common etiology in the U.S., and Kawasaki disease is the most common etiology in the Far East (Cohen & Ogara, 2008). Atherosclerosis is responsible for more than 50% of CAAs in adults in the Western world, whereas Kawasaki disease, which is characterized by an acute, self-limited vasculitis occurring in childhood, may lead to the development of CAAs in 15 to 25% of untreated children (Falsetti & Carrol, 1976; Pahlavan & Niroomand, 2006). Other causes of CAAs include inflammatory arterial diseases (polyarteritis nodosa, syphilis, Takayasu arteritis, Behçet’s disease), connective tissue disorders (systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, scleroderma), hereditary collagen defects (Marfan syndrome, Ehlers-Danlos syndrome), coronary artery revascularization procedures (balloon angioplasty and laser atherectomy), candidiasis, chest traumas, and primary hyperaldosteronism (Alford et al., 1976; Antoniadis et al., 2008). CAA have also been noted in conjunction with infection, drug use, trauma, and percutaneous coronary intervention (Pahlavan & Niroomand, 2006). Therefore, many inflammatory disorders and infectious etiologies have been associated with CAAs. The etiologies usually vary according to the geographic location and age of the patient (Díaz-Zamudio et al., 2009).

Atherosclerosis
Kawasaki disease
Congenital
Arteritis (polyarteritis nodosa, syphilis, systemic lupus erythematosus, Takayasu arteritis
disease, Behçet’s disease)
Mycotic
Dissection
Chest trauma
Drugs
Connective tissue disorders (SLE, rheumatoid arthritis, ankylosing spondylitis,
scleroderma)
Hereditary collagen defects (Marfan and Ehlers-Danlos syndromes)
Metastatic tumor
Coronary angioplasty (balloon, laser atherectomy, stent implantation, directional coronary
atherectomy, pulsed laser coronary angioplasty and brachytherapy)*


Table 3. Etiology of Coronary Artery Aneurysms.

The following sections describe the primary causes of CAA.

5.1 Atherosclerosis

Atherosclerosis is the most common cause of morbidity and mortality worldwide. This
disease is characterized by chronic inflammatory and intimal lesions, called atheromas or
fibrofatty plaques, which protrude into the lumen, weaken the underlying media and undergo a series of complications affecting primarily elastic arteries and larger and medium sized muscular arteries, such as coronary arteries (Libby, 2002). Dauod et al. (1963) believed that aneurysms are formed as a result of poststenotic transformation of kinetic energy to potential energy and pressure abnormalities in the vessel. Moreover, Siouffi et al. (1984) have explained that the elevated velocity of blood flow, which results in increased shear stress at the stenotic site, can promote endothelial injury and poststenotic vasodilation. In contrast, atherosclerotic plaque borders have been suggested to be potential foci of plaque disruption and thrombus formation, which cause microcirculation impairment and clinical symptoms of ischemia. The atherosclerotic material located at the injured site presumably can act as the point of aneurysm formation (Berkoff & Rowe, 1975; Befeler et al., 1977). However, a theory from Markis et al. (1976) has suggested that the formation of the atherosclerotic aneurysm occurs as a result of an imbalance between the intravascular pressure and the elasticity of the vascular wall. In atherosclerosis, the vascular inflammation and plaques are distributed at near side branches or arterial stenosis (where blood flow is nonuniform) and at the lesser curvature of bends (where the blood flow rate is relatively low). Blood flow exerts shear stress on the vessel wall by altering cell physiology via several mechanisms. Shear stress also arises at the interplay between blood and the endothelial layer, where it induces a shearing deformation of the endothelial cells. Regions of the arterial tree with uniform geometry exert a physiologic shear stress, whereas arches and branches are exposed to a disturbed, oscillatory flow, which exerts low shear. Atherosclerotic lesions occur predominantly at sites of low shear, whereas regions of the vasculature exposed to a physiologic shear are protected (Koskinas et al, 2009). The occurrence of atherosclerotic lesions in the human carotid bifurcation, abdominal aorta and coronary artery strongly correlates with low shear regions experiencing an almost purely oscillatory flow (Moore et al., 1994). Atherosclerotic lesions are more frequent in the proximal portions of the three major coronary arteries (mainly the RCA). These data confirm that the coronary bifurcation pattern predisposes to the development of atherosclerotic lesions due to low endothelial shear stress. These atherosclerotic plaques develop in areas in which low endothelial shear stress occurs, inducing aneurysm formation as a result of endothelial damage (Chatzizisis et al., 2008). Inflammatory cells residing in the plaque (lymphocytes, macrophages, and foam cells) play an important role in the evolution and complication of atherosclerosis. These cells secrete cytokines that further amplify inflammation and produce proteases, such as metalloproteinase (MMPs) that destabilize the plaque by damaging the extracellular matrix (elastin) and thinning the fibrous cap (Libby, 2002). The result of elastin degradation is increased wall stiffness, elongation, and tortuosity of the vessel leading to areas of turbulent flow, which in combination with endothelial injury, favors the thrombus formation that is seen in most aneurysms (Hans et al., 2005).

Microscopic evaluation of the atherosclerotic aneurysmal wall usually demonstrates typical components of atherosclerotic plaques, such as mononuclear cells infiltrates, lipid deposits, cholesterol crystals, destruction of the intima and media, diffuse hyalinization, focal fibrosis, calcification of the media, intramural hemorrhage and sometimes a foreign-body giant cell reaction (Markis et al., 1976). A representative autopsy case is shown in the Figure 1.
Novel Strategies in Ischemic Heart Disease

Fig. 1. (A) Anterior view of the heart. Note a giant CAA (6x6.2x7.5 cm) starting after a 10-mm-long segment of normal-sized RCA giving off the aorta and pushing back the right atrium. (B) Posterior view of the heart. The coronary aneurysm finishes as a 5-cm-long ecstatic arterial segment of the RCA along the atrioventricular groove to give off the posterior descending artery in the interventricular groove. In (A) and (B), the epicardium was removed to better show the diffuse atherosclerotic coronary artery disease (*). (C) Coronal section of the heart. The coronary aneurysm was empty and the wall was thickened with lipid deposits. Bar = 5cm. Microscopic section of the CAA wall. Note the dense fibrocollagenous thickening, extracellular lipids, mononuclear cells, and lymphocytic inflammatory infiltrates in the aneurysmal wall (D; Hematoxylin-eosin) and (E; Masson’s trichrome). Bar = 1mm. Ao: Aorta; CAA: coronary artery aneurysm; LA: left atrium; LV: left ventricle; PT: pulmonary trunk; RA: right atrium; RCA: right coronary artery, and RV: right ventricle.

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5.2 Coronary vasculitis

Systemic vasculitis represents a large group of diseases that are defined as inflammatory lesions of blood vessels (Lightfoot et al., 1990). Inflammatory thickening of the coronary arteries may lead to their occlusion, weakness of the wall, and in some cases, the development of aneurysms.

5.2.1 Kawasaki Disease (KD)

KD or mucocutaneous lymph node syndrome, is the most common cause of CAA in children and the second most common in adults. KD is a multisystem inflammatory illness that predominately affects children 6 months to 5 years of age, although younger infants and older children can also develop the illness (Amano et al., 1979). KD can result in acute vasculitis, most strikingly of the coronary arteries (Newburger et al., 1986). Important complications include coronary artery dilation and aneurysm formation, which occurs in 10–15% of patients during the acute stage. The incidence of KD is at least ten times higher in Japan than in Western populations (Nakamura et al., 2008). Siblings of children with KD have a tenfold higher risk of developing the illness than the general population, and children whose parents had KD have a twofold increased incidence (Uehara et al., 2003).

The etiology of KD remains a major pediatric enigma, despite efforts to identify the cause over the last four decades. Many proposed etiologies of KD have been suggested since Dr. Tomisaku Kawasaki’s initial description of the illness in Japan in the 1960s (Kawasaki, 1967). The most widely proposed theories have fallen under the categories of environmental toxin exposure, autoimmune pathogenesis, and infectious diseases. Because the clinical and epidemiologic features of KD support an infectious cause, one speculation is that the infectious agent travels from its portal of entry through the bloodstream and infects many organs and tissues; the immune response then targets these sites of infection. The theory of KD etiology that best fits the available data is that a ubiquitous infectious agent results in asymptomatic infection in most individuals but causes KD in a subset of genetically predisposed individuals (Rowley et al., 2008). Up to 25% of untreated children will develop persistent abnormalities in the coronary arteries; however, therapy with intravenous gammaglobulin and aspirin within the first ten days of fever onset reduces the prevalence of coronary artery abnormalities to approximately 5% (Newburger et al., 1986).

Inflamed tissues in acute KD show inflammatory cell infiltration of the arterial wall (mononuclear cells, lymphocytes, and macrophages), destruction of the internal elastic lamina, necrosis of smooth muscle cells, myointimal proliferation and subsequent occurrence of dilations or aneurysms (Burgner et al., 2009). Histopathological findings have indicated destruction of coronary artery walls with diffuse vasculitis, raising the possibility that MMPs are also involved in coronary arterial wall destruction and the formation of CAAs (Amano et al., 1979). Among patients with KD, those with coronary artery lesions have higher plasma levels of both MMP 3 and MMP 9. Within the arterial wall, the production of MMPs and other enzymes by macrophages results in the destruction of collagen and elastin fibers. The wall can lose its structural integrity and dilate or balloon, forming an aneurysm. The immune response is ultimately successful in controlling the pathogen, but damage to the coronary arteries may have already occurred (Yilmaz et al., 2007).

The diagnosis of KD is clinical and is based on the major clinical features of the acute phase. Undoubtedly, many asymptomatic adult patients with coronary arterial lesions caused by
KD remain undiagnosed, forming a hidden cohort with this disease (Tsuda et al., 2007). Even once acute KD was recognized, the diagnosis of complicating coronary artery lesions was more difficult in the sixties and seventies. Symptoms are rare in this population until the onset of acute coronary syndrome; consequently, the presence of coronary artery disease is unsuspected in most patients. Only recently have technical developments allowed the detailed examination of coronary artery morphology.

Although the precise etiology and pathogenesis of KD are not completely understood, the current management of acute KD is based upon prospective, controlled, multicenter treatment trials that have clearly demonstrated the efficacy of intravenous immunoglobulin (IVIG) and high-dose aspirin to halt inflammation and reduce the likelihood of the development of coronary abnormalities when administered by the tenth day of illness (Newburger et al., 1991). Whether or not to continue antithrombotic therapy in patients with regressed giant aneurysms is an important problem to resolve in the future (Tsuda et al., 2010).

5.2.2 Polyarteritis nodosa (PAN)

For decades, most forms of vasculitis were termed periarteritis nodosa. Newly recognized types of this disease were characterized and classified according to features that were similar to or distinct from those of PAN (Klinger, 1931; Churg & Strauss, 1951). In the early 1900s, Ferrari (1903) and Dickson (1908) proposed the name polyarteritis nodosa, partly to distinguish the disorder described by Kussmaul & Maier (1866) from the vascular lesion of tertiary syphilis. Furthermore, the term polyarteritis nodosa emphasizes the panarteritic nature of this disease and underscores the fact that multiple arteries are affected by the process (Arkin, 1930). PAN is one of a spectrum of diseases that belong to the pathologic category of necrotizing vasculitis. The classic form of PAN was described by Kussmaul & Maier in 1866 as consisting of focal panmural, necrotizing inflammatory lesions in small- and medium-sized arteries and characterized by fibrinoid necrosis and infiltration of predominantly polymorphonuclear leukocytes. PAN is a multiple organ disorder with characteristic involvement of the renal and other visceral arteries. Coronary artery involvement (76%) ranks second in frequency behind the renal arteries (85%) (Lypsky et al., 1994). Thrombosis, aneurysms, and arteritis of the coronary vessels are known complications of the disease. PAN affects 2 to 6 people per 100,000 per year and can be seen in all ethnic groups. Any age group can be affected, but the disease occurs more commonly in men than in women (2:1) and is seen in people between the ages of 40 and 60 years. The cause of PAN is unknown for most patients. For years, an infectious etiology for PAN has been considered. Early observers considered streptococci or Staphylococcus aureus to be likely candidates (David et al., 1993). Hepatitis B surface antigenemia (with immune complex formation) has been reported to be associated with approximately 20% of patients with PAN (Trepo et al., 1974). The incidence is higher in areas where hepatitis B is endemic. In studies from France, the percentage of cases of PAN attributed to hepatitis B viral infection decreased from 36% to 7% during the past decade after the development of vaccines against viral hepatitis (Guillevin et al., 1996).

Aneurysms often form at the branching points of small- and medium-sized arteries and occur in 9% of patients with PAN (Kastner et al., 2000). The rupture of aneurysms may result in spontaneous hemorrhage in approximately 6% of cases (Zizic et al., 1982). Acute lesions in PAN swiftly evolve into a panarteritis with degeneration of the arterial wall, destruction of the external and internal elastic lamina, and fibrinoid necrosis. The cellular
infiltrate is pleomorphic, with both polymorphonuclear cells and lymphocytes present to various degrees at different stages. Degranulation of neutrophils within and around the arterial wall leads to leukocytoclasis. In time, this inflammation leads to transmural necrosis and a homogeneous, eosinophilic appearance of the blood vessel wall (fibrinoid necrosis). The vascular wall inflammation in PAN may be strikingly segmental, affecting only part of the circumference of a given artery. Segmental necrosis, in turn, leads to aneurysm formation. During later stages, complete occlusion may occur secondary to endothelial proliferation and thrombosis. Throughout involved tissues, the coexistence of acute and healed lesions is typical. Features of granulomatous vasculitis are absent. Acute PAN evolves into a sclerotic process with fibrosis of the damaged arterial wall and mesenchymal organization. In some cases, there is also recanalization of thrombi. Chronic arterial narrowing may result (Stone, 2002).

The identification of PAN can be a clinical challenge given its varied spectrum of organ involvement, wide range of clinical symptoms, and variations in severity. The clinical course can last from months to years, and relapse occurs in 40% of treated patients with a median interval of 33 months (Gordon et al., 1993). If untreated, the disease may have a fulminant course; the 5-year survival is less than 15%. However, survival increases to 80% with steroid treatment, with or without cytotoxic drugs (Guillevin et al., 1996). Symptoms, such as fever, malaise, and weight loss, are common, and up to 70% of patients have abdominal pain, nausea, vomiting, and infarction are uncommon, occurring in 1% of cases (Zizic et al., 1982).

A combination of corticosteroids and immunosuppressants is a highly effective therapy for progressive PAN. Therefore, early diagnosis, which is usually based on clinical signs and symptoms and laboratory and angiographic findings, is crucial for the prognosis of the patient (Parangui et al., 1991). Arterial angiography is still an important measure in cases suggestive of PAN when other noninvasive tests do not allow diagnosis. The diagnosis of PAN is strongly indicated by the finding of aneurysms within the vasculature during angiography (Holzknecht et al., 1997). Early diagnosis and treatment of PAN are necessary to prevent serious organ damage and should be suspected in patients with febrile disease, weight loss, and evidence of multiple organ involvement. The diagnostic criteria have been classified by the American College of Rheumatology (Ewald et al., 1987). Three of 10 criteria must be present for the diagnosis of PAN, and positive angiography is one of the criteria. In symptomatic patients (with primarily abdominal complaints, nephropathy, hypertension, or generalized malaise), angiography is a valuable diagnostic tool that can lead to the diagnosis in occult cases. Angiographic findings, including aneurysms, ectasia, or occlusive disease, are present in approximately 40%–90% of patients at the time clinical symptoms appear (Hekali et al., 1991).

Some case reports of coronary angiograms performed in patients with PAN have been published. Przyborski (1981) has described a 29-year-old man for whom the coronary angiography revealed a diffusely aneurysmal RCA with severe obstructive lesions in the left circumflex and left anterior descending arteries. PAN was subsequently diagnosed by a skeletal muscle biopsy. The biopsy showed fibrinoid necrosis affecting connective tissue and blood vessels in the muscle epimysium and adjacent fascia, which are features that are characteristic of a collagen vascular disease such as PAN. Pick et al. (1982) have reported a 26-year-old woman who, during cardiac catheterization, revealed numerous aneurysms involving all three coronary vessels that were particularly worse in the distal RCA. Cassling
et al. (1985) have described a 30-year-old female smoker who presented with intermittent chest pain and a strongly positive stress test. Coronary angiography revealed severe luminal narrowing of several coronary arteries without aneurysm formation. The clinical diagnosis was occlusive atherosclerotic coronary artery disease. The patient died intraoperatively after the anastomosis of coronary artery bypass grafts. Subsequent autopsy revealed an unexpected coronary adventitial thickening and a polymorphous lymphocytic infiltrate consistent with PAN. An autopsy case of PAN is shown in the Figure 2.

For cases of idiopathic PAN, corticosteroids and cytotoxic agents remain the cornerstones of treatment (Guillevin et al., 1996). Approximately half of patients with PAN achieve remissions or cures with high doses of corticosteroids alone (Lam et al., 1981). Fortunately, the availability of effective antiviral agents has revolutionized the treatment of hepatitis B virus (HBV) infection-associated cases in recent years (Guillevin et al., 1996). Prophylactic treatment of large aneurysms by means of catheter embolization should be considered in anticipation of the risk of rupture. Aortography may not adequately substitute for selective injections of the viscera, but the retroperitoneal branches are depicted, and they can also be involved with aneurysms that may rupture in rare cases. In a small percentage of patients with PAN, aneurysm rupture in an organ or retroperitoneal branch may be the first clinical evidence of the disease. Embolization therapy is often the treatment of choice (Hachulla et al., 1993). The presence of aneurysms may relate to the phase of the disease or its severity. Arterial segments of ectasia may be either a precursor to a fully expanded aneurysm or a phase in the healing process. Aneurysms of PAN may resolve over time as remission occurs (Guillevin et al., 1996).

Fig. 2. (A) Right posterolateral view of the heart of a 56-year-old woman with systemic PAN. Note the multiple aneurysms in coronary arterial tree. (B) Detail of aneurysmal nodules in the right marginal artery (arrows). Histopathology of the coronary artery (C), showing an important luminal occlusion by intimal proliferation, partial disruption of the internal elastic laminae and tunica media, intense inflammatory infiltrate and remarkable adventitial fibrotic thickening (C; Hematoxylin–eosin and D; Masson’s trichrome). Bar = 1mm. PAN: Polyarteritis Nodosa.
5.2.3 Takayasu arteritis

Takayasu arteritis (TA) was first described in 1908 by the Japanese ophthalmologist Takayasu, who reported ocular changes, such as aneurysms and arteriovenous anastomoses, in patients with this disease. This primary systemic vasculitis is a group of autoimmune syndromes characterized by stenosis, occlusion, or aneurysmal dilation that involves the large cardiac vessels, chiefly the aorta and its main branches. Epidemiological data have demonstrated that TA is more common in Asian countries than in other parts of the world. The incidence of aneurysms in patients with TA has been reported to be approximately 18% and 24%, and approximately 150 new cases per year have been estimated in Japan. However, the disease may be found worldwide, including occidental countries (Subramanyan et al., 1989). TA primarily affects females, and the female to male ratio can reach up to 8:1 in adulthood (age ≤40 yr); in childhood, the ratio is significantly lower at 2:1 (Sharma et al., 1996; Mesquita et al., 1998). The etiology of TA remains unknown, although autoimmune mechanisms and infections are factors that have been reported to be associated with the disease. Genetic aspects also appear to contribute to the pathogenesis of TA (Buzaid et al., 1995).

The clinical progression of TA can be divided into acute and chronic phases. The acute phase comprises signs and symptoms of a systemic inflammatory process, such as fever, weight loss, anorexia, fainting, dizziness, nocturnal sweating, myalgia, arthralgia/arthritis, exanthema, abdominal pain, vomiting and anemia. The chronic phase is characterized by symptomatology of vascular occlusion with the appearance of hypertension and changes in peripheral pulses (Morales et al., 1991). However, these phases are not always distinct and may occur simultaneously (Kerr, 1995). Most of the lesions cause luminal narrowing, which can lead to occlusion; however, coronary aneurysms are extremely rare. CAA can develop as vascular walls weaken because of arterial hypertension and the extensive destruction of elastic fibers in the media. CAA often cause stasis of blood flow and result in mural thrombus (Lie, 1998). The histological changes are characterized by marked thickening of the adventitia, media, and intima (Subramanyan et al., 1989). The inflammatory process involves the coronary arteries in less than 10% of patients, mostly in the form of stenotic lesions (Sharma et al., 1995), and can be divided into 3 distinct morphologic types: stenosis or occlusion of the coronary ostia, diffuse or focal coronary arteritis, and coronary aneurysm formation (Panja et al., 1998). Rarely, the inflamed aorta of TA can be a source of dissection, but the various symptoms and signs more commonly mimic an aortic dissection (Reichman & Weber, 2004).

Diagnosis is difficult because the initial stage of the disease may be asymptomatic or may be characterized by the presence of signs and symptoms of the acute phase. The latter may lead to an erroneous diagnosis, such as rheumatic fever, juvenile rheumatoid arthritis or systemic lupus erythematosus (Kerr, 1995). Angiography and clinical examination remain the cornerstones for the diagnosis of TA. While arteriographic studies of the aortic and pulmonary territories are necessary to obtain a complete sense of the extent of the disease, these invasive techniques cannot be frequently repeated (Hata et al., 1996). Echocardiography has become a valuable noninvasive diagnostic technique for the detection of cardiovascular complications in patients with TA (Soto et al., 1996). The use of drug-eluting stents for the effective treatment of coronary lesions associated with TA (Kang et al., 2006). However, surgical treatment of TA poses many difficulties related to the timing of the operation, the techniques and materials used, and postoperative management. Even though TA is considered a severe disease, it rarely causes death (Kerr, 1995). Nevertheless, the outcome depends on the medical and surgical
treatment and on the cardiac involvement, severity, type of arterial hypertension and distribution of the vascular lesions (Mesquita et al., 1998). Currently, all treatment remains symptomatic because the etiology and pathogenesis of the disease are as yet unknown (Buzaid et al., 1985). Corticosteroids are the most widely employed drugs for the treatment of TA, and because they suppress the inflammatory manifestations and are helpful in the reversal of arterial stenosis, they are administered at high doses during the initial stage of the disease. Other drugs, such as cyclophosphamide, methotrexate and cyclosporin have been indicated for patients who do not respond to corticotherapy (Mesquita et al., 1998). An autopsy case is demonstrated in the Figure 3.

Fig. 3. (A) Anterior and (B) posterior view of the heart, aorta and the major thoracic branches of a 17-year-old female diagnosed with Takayasu arteritis. Bar = 2.5cm. (C) Detail of the important luminal occlusion of the major thoracic arteries. (D) Histopathological view of the right carotid showing intimal thickening and partially recanalized thrombus. Hematoxylin-eosin; Bar = 1 mm. (E) RCA transversely sectioned to show the stenotic lumen. (F) Histopathological view of the RCA showing intimal thickening, partially recanalized thrombus and prominent adventitial involvement. Hematoxylin-eosin; Bar = 1 mm.
5.3 Miscellaneous

In addition to those described above, some other diseases are also involved in the formation of CAA. Connective tissue diseases, such as Marfan syndrome, can cause aneurysms without atherosclerosis. Marfan syndrome is associated with mutations in the gene for fibrillin that is homologous to the family of latent TGF-β binding proteins, which hold TGF-β in an inactive complex (Gelb, 2006). Cystic medial degeneration is a common feature of the aneurysms in Marfan syndrome, so its presence in a CAA may be indicative of a congenital genetic defect that causes an excess of active TGF-β. However, cystic medial degeneration is also commonly seen in the aortic aneurysms of late middle-aged and elderly patients without Marfan syndrome, but this degeneration could be indicative of excess active TGF-β in these patients as well. TGF-β can be inhibited by angiotensin II type 1-receptor antagonists, such as losartan, which can prevent aortic aneurysms in a mouse model of Marfan syndrome (Habashi et al., 2006).

Systemic lupus erythematosus commonly causes arteritis, are rare and is most common in women of African descent who are of childbearing age (Matayoshi et al., 1999). Generally, these aneurysms are large and proximal and are in the setting of other obvious clinical markers of systemic disease. Clinical signs may include serositis, hematologic abnormalities, renal disease, dermatologic findings, abdominal angina, and neurologic findings, such as weakness, central nervous system vasculitis, and radiculopathy. In mycotic aneurysms, the injury and destruction of the tunica media may be due to microembolization to the vasa vasorum, direct pathogen invasion of the arterial wall, or immune complex deposition (Ford et al., 2007). Traumatic and iatrogenic aneurysms are frequently pseudoaneurysms. The pathogenesis of aneurysm formation after catheter-based interventions is not fully understood (Bjorn-Hansen et al., 1989). This consequence has been attributed to the use of an oversized balloon, high inflation pressures, coronary dissection, interventions in the setting of acute myocardial infarction, and inadequate healing due to antiproliferative treatment with cortisone, colchicine, and anti-inflammatory drugs (Vassanelli et al., 1989).

Recently, with the advent of implantation of drug-eluting stents, increasing numbers of reports have suggested that stents can cause CAA months or years after the procedure (Pahlavan & Niroomand, 2006; Nichols et al., 2008). The drug-eluting stent contains an immunosuppressant, such as Sirolimus, which inhibits inflammation, or chemotherapeutic agents, such as Paclitaxel, which is an anti-inflammatory agent that inhibits cell proliferation. In due course, once the drug is eluted, the polymer in which the drug is embedded may elicit a hypersensitivity reaction and vasculitis and result in weakening of the vessel wall and subsequent dilatation (Manghat et al., 2006). Mechanical damage to the arterial wall during balloon angioplasty and stent placement or turbulent blood flow may be an added factor for the development of an aneurysm (Nichols et al., 2008). This concept is supported by the finding of an eosinophilic infiltrate in the few cases of such post-stent CAA that have been examined histologically (Virmani et al. 2004). Patients with a history of cocaine abuse have an increased prevalence of CAA (30.4%). These patients appear to be at increased risk of acute myocardial infarction. Several mechanisms have been proposed for the development of aneurysms related to cocaine abuse. These include (a) direct endothelial...
damage caused by severe episodic hypertension and vasoconstriction and (b) underlying atherosclerosis (Satran et al., 2005).

6. Pathogenesis

The pathogenesis of CAA is not completely understood but is likely to involve the destruction of the arterial media, thinning of the arterial wall, increased wall stress, and progressive dilatation of the coronary artery segment (Hirsch et al., 2000). Inflammation spilling over into the tunica media from the tunica intima has been hypothesized to link atherosclerosis to aneurysm formation in susceptible individuals. One could hypothesize that the giant cells that are sometimes present in CAA are merely reacting to cholesterol from atheroma and erythrocyte breakdown in the adjacent tunica intima. The lymphohistiocytic inflammation is merely spillover from the atherosclerosis in the adjacent tunica media. The cystic medial degeneration and aneurysm formation may be merely side effects of this spillover inflammation. Alternatively, one could hypothesize that the inflammation is sometimes due to autoimmune vasculitis coexisting with the atherosclerosis (Nichols et al., 2008).

Aneurysm development can be a systemic or local disorder characterized by the overexpression of pro-inflammatory cytokines and enzymes that are capable of degrading elastin and other components of the vascular wall. The pathophysiology is focal destruction of the internal elastic lamina with early neutrophil infiltration followed by macrophages and cytotoxic T lymphocytes (Takahashi et al., 2005). Increased proteolysis of extracellular matrix proteins is probably a mechanism of CAA formation (Mata et al., 2011). MMPs (1, 2, 3, 9 and 12) are capable of degrading essentially all components of the arterial wall matrix (elastin, collagen, proteoglycans, laminin, fibronectin, etc.) and are present at elevated concentrations in aneurysms, while decreased levels of tissue inhibitors of MMPs are present. The MMP-3, 5A allele is associated with higher promoter activity for transcription of the gene, and this allele is more common in patients with CAA plus atherosclerosis than patients with only coronary atherosclerosis (Lamblin et al., 2005). CAAs have destruction of the tunica media, which is thinned, sometimes markedly, sometimes to the point of no longer being identifiable between the tunica intima and tunica adventitia. The normal smooth muscle cells and elastic fibers are replaced by hyalinized connective tissue. Destruction of the internal elastic lamina sometimes obscures the border between diseased tunica media and tunica intima diseased with atherosclerosis. Lipid deposits, foam cells, cholesterol clefts, eosinophilic debris, calcifications, neovascularization, inflammatory reactions, and sometimes hemorrhages can be seen and are sometimes limited to the tunica intima with atherosclerosis, sometimes extend into the tunica media and sometimes spread into the indistinct border zone. The inflammatory reaction chiefly consists of lymphocytes but can also include macrophages and sometimes foreign body giant cell formation around cholesterol clefts. Neutrophils, eosinophils, and plasma cells can be part of the inflammation. This inflammatory reaction is sometimes present in multiple arterial tunica and is sometimes transmural, involving all 3 layers of the artery. Thrombus formation is invariably present on the luminal surface of coronary aneurysms (Daoud et al., 1963).
Table 4. Cause, Age, Summary Description and Principal Pathogenetic Mechanisms of Coronary Artery Aneurysms

<table>
<thead>
<tr>
<th>Cause</th>
<th>Age</th>
<th>Description</th>
<th>Pathogenetic Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis</td>
<td>Adults</td>
<td>Most common cause of CAA, clinical importance depends on association with significant coronary artery stenosis</td>
<td>Local mechanical stress from stenosis, atherosclerotic pathologic findings extending into tunica media</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Childhood</td>
<td>Most common cause of CAA in childhood in Japan, spontaneous resolution occurs in 50%</td>
<td>Autoimmune, vasculitis</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>Childhood</td>
<td>Common cause of CAA in young Asian females in Japan</td>
<td>Cellular immunity associated with chronic infection</td>
</tr>
<tr>
<td>Takayasu</td>
<td>Young adults</td>
<td>Necrotizing inflammatory lesions in small- and medium-sized arteries</td>
<td>Characterized by fibrinoid necrosis and infiltration by predominantly polymorphonuclear leukocytes</td>
</tr>
<tr>
<td>Polyarteritis Nodosa</td>
<td>Young adults</td>
<td>Ehlers-Danlos syndrome, Marfan syndrome, cystic medial necrosis</td>
<td>IL-6, TGF-β, C-reactive protein, MMP-2, MMP-9</td>
</tr>
<tr>
<td>Connective tissue disorders</td>
<td>Young adults</td>
<td>Infection with Staphylococcus aureus or Pseudomonas aeruginosa, syphilis, Lyme disease</td>
<td>Microembolization to vasa vasorum, direct pathogen invasion of arterial wall, immune complex deposition</td>
</tr>
<tr>
<td>Myotic</td>
<td>Any age</td>
<td>Clinical history helps establish diagnosis healing because of antiproliferative treatment with cortisone, colchicine, and anti-inflammatory drugs</td>
<td>Trauma from oversized balloon or high inflation pressures, coronary dissection, interventions in the setting of acute myocardial infarction, inadequate</td>
</tr>
<tr>
<td>Trauma/iatrogenic</td>
<td>Adults</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified from Diaz-Zamudio et al., 2009.

7. Clinical manifestations and complications

In most cases, CAAs are asymptomatic; then when symptomatic, the clinical manifestations depend on the underlying cause. Although CAA can be seen at any age, those that were related to atherosclerosis usually appear later in life than those of a congenital or inflammatory nature.

No clinical feature characteristics exist for atherosclerotic CAAs. The clinical manifestations are similar to those seen in coronary artery disease (Tunick et al., 1990), and the patients may have angina pectoris, dyspnea, edema, myocardial infarction and sudden death (Pappy et al., 2011). Occasionally, a systolic murmur is heard over the precordium. An association with an abdominal aortic aneurysm and hypertension can occur. Large aneurysms,
particularly those that are partially or completely filled with mural thrombi, may create
diagnostic challenges by masquerading as cardiac masses (Ramos et al., 2008). The main
differential diagnoses include pericardial cysts and primary and metastatic tumors (Tunick
et al., 1990). Transesophageal echocardiography and magnetic resonance imaging can add
valuable diagnostic information; however, in many cases, diagnosis is not achieved until
open-heart surgery.

Factors that can contribute to development of complications are: distal embolization with
myocardial ischemia, rupture with associated fistula, cardiac tamponade or
hemopericardium, thrombosis, dissection, vasospasm and vessel compression (Syed &
Lesch, 1997; Díaz-Zamudio et al., 2009).

8. Diagnosis

CAA may be detected by non-invasive tools, including echocardiography, computed
tomography, and magnetic resonance imaging, but coronary angiography remains the best
method for the assessment of coronary anatomy and pathology (Pahlavan & Niroomand,
2006). Coronary angiography provides additional information regarding the size, shape,
location and the number of existing anomalies and show an image of the coronary artery
status (Gziut & Gil, 2008), determining the extent and severity of the coronary lumen
obstruction in coronary artery disease (Scanlon et al., 1999). Multidetector row computed
tomography (MDCT) technology, have led to widespread enthusiasm for the use of
noninvasive coronary angiography (Hendel et al., 2006). The three dimensional evaluation
helps to provide an easy understanding of complex anatomic structures and allows the
analysis of the lumen and the vessel wall and the identification of thrombi and associated
plaque formation. Other non-invasive methods can be also helpful in the diagnosis of
aneurysms, including bidimensional transthoracic echocardiography, transesophageal
echocardiography (Gziut & Gil, 2008) and electrocardiographic-gated scans, which is a dose
modulation technique. These methods are recommended to minimize radiation dose and
represent promising tools for the evaluation of children (Goz & Cakir, 2007), particularly
children with Kawasaki disease (Beiser et al., 1998). Magnetic resonance (MR) angiography
is an alternative for patients for whom exposure to repetitive radiation from multidetector
CT is not wanted and for whom other noninvasive modalities are not suitable (Mavrogeni et
al., 2004). However, these methods allow the investigation of only the proximal segments of
the coronary arteries. Other modalities (such as intravascular ultrasound, Doppler flow
wire, and pressure with for calculation of fractional flow reserve) can be incorporated into
the invasive evaluation (e.g., angiography), and the pathology can often be treated during
the same procedure. Multidetector-row computed tomography (MDCT), a technology that
allows good noninvasive imaging of the coronary arteries, has been used despite of its
indications and a still-to-be-defined role in the management of patients with cardiovascular
symptoms (Zimmet & Miller., 2006).

Undoubtedly, invasive coronary angiography remains the “gold standard” for the
evaluation of CAA for a number of reasons. Only blood flow within the lumen can be
evaluated, and conventional invasive coronary angiography provides no information about
the vessel wall. Thus, with conventional coronary angiography, the true size of the
aneurysm may be underestimated or the aneurysm may not even be seen when it is
occluded or contains substantial thrombi or plaque (LaMotte & Mathur, 2000).
9. Treatment

CAA treatment consists of medical management, surgical resection, and stent placement; however, the appropriate treatment for CAAs is controversial and depends on the particular clinical situation. The recently available results have been based primarily on case reports and not on controlled studies, which continue to cause a therapeutic dilemma. The medically conservative therapy generally consists of attempts to prevent thromboembolic complications in patients with aneurysmal arteries who are at increased thrombotic risk through administration of antiplatelet and anticoagulant medication (Demopoulos et al., 1997). The use of anticoagulants is based on the observations of thrombus formation in association with CAA and its distal embolization. Surgical management is appropriate in symptomatic patients who have obstructive coronary artery disease or evidence of embolization leading to myocardial ischemia and in patients with CAAs with a risk of rupture (LaMotte & Mathur, 2000). Recently, percutaneous application of polytetrafluoroethylene (PTFE)-covered stents has gained popularity due their ability to effectively limit the expansion of CAAs by reducing blood flow within the aneurysm, thereby preventing their rupture. Some authors have suggested that PTFE-covered stents should be limited to patients whose aneurysms are < 10 mm in diameter (Cohen & O’Gara, 2008). Percutaneous strategies also include coil embolization, autologous saphenous vein-covered stent grafting, and one case report of DES implantation superimposed on a PTFE-covered stent graft (Ghanta et al., 2007).

Surgical strategies that have been described include aneurysm ligation, resection, marsupialization with interposition graft, and coronary artery bypass surgery. The majority of the experience regarding the aforementioned strategies stem from atherosclerosis-induced CAAs (Antelmi et al., 1993). Some surgeons believe that surgical repair is mandatory when a coronary aneurysm is 3 times larger than the original vessel diameter. A complete surgical resection or stent placement may be performed, depending on the presence or absence of coexisting obstructive coronary artery disease. Another surgical option that is frequently used is coronary artery bypass graft (CABG) followed by the ligation or resection of the aneurysm. This approach is indicated in patients who have larger aneurysms that are at higher risk of rupture (Myler et al., 1991).

However, special consideration must be taken when an immunoinflammatory condition is involved. Treatment strategies to improve outcomes in vasculitis-induced CAA involve the use of immunosuppressive therapy to abate the underlying inflammatory process. The role of catheter-based intervention needs to be further explored in this particular patient population. It must be emphasized that there is no consensus regarding how coronary lesions related to systemic inflammatory diseases should be treated (Pappy et al., 2011). Currently, no treatment of CAAs has been universally accepted due to their low incidence and the lack of controlled clinical trials.

10. Conclusion

CAA is an uncommon and often accidental finding. CAAs are usually associated with atherosclerosis in adults in Western countries, while Kawasaki disease is the most common cause of CAA in Japan and in children or young adults. Nevertheless, the exact mechanisms leading to CAA formation are still unclear. Unfortunately, the lack of specific prodromal
symptoms or factors predisposing to the formation of CAAs significantly limits the diagnostic possibilities, and consequently, the therapeutic modalities. One way to improve the understanding of the pathogenesis of aneurysms can be through the development of experimental models, such as those that are used for studying abdominal aortic aneurysms (Mata et al., 2011). Thus, this review aimed to provide an update on the pathogenesis and treatment of CAAs to highlight for physicians and thoracic surgeons the practical management of patients with this disease and to help avoid major complications, such as death.

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12. References


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The first edition of this book will provide a comprehensive overview of ischemic heart disease, including epidemiology, risk factors, pathogenesis, clinical presentation, diagnostic tests, differential diagnosis, treatment, complications and prognosis. Also discussed are current treatment options, protocols and diagnostic procedures, as well as the latest advances in the field. The book will serve as a cutting-edge point of reference for the basic or clinical researcher, and any clinician involved in the diagnosis and management of ischemic heart disease. This book is essentially designed to fill the vital gap existing between these practices, to provide a textbook that is substantial and readable, compact and reasonably comprehensive, and to provide an excellent blend of "basics to bedside and beyond" in the field of ischemic heart disease. The book also covers the future novel treatment strategies, focusing on the basic scientific and clinical aspects of the diagnosis and management of ischemic heart disease.

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