Editorial

Newer Concepts Regarding Adults With Coronary Artery Aneurysms

Are They All Kawasaki? Does It Make a Difference?

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The most commonly accepted definition of coronary aneurysm (CA) is an enlargement of a coronary arterial segment to 50% of the distal reference diameter.[1,2] This definition generally refers to the inner diameters of the vessels as determined by coronary angiography. Computerized axial tomographic imaging is currently the preferred method of studying CA, especially for longitudinal studies of the extent and severity of dilatation, calcification, mural thrombosis, and stenosis.[3] Only tomographic imaging can quantitatively describe vascular wall thickening, a hallmark of the disease progression and prognosis in a postarteritis CA.

Additionally, the 50% definition can be inaccurate: In cases with diffuse dilatation, the reference diameter can become difficult to identify.[2] The 50% rule may or may not carry prognostic value, which is the main clinical goal of classifying a coronary segment as ectasic or anomalous. The essential clinical interest is in differentiating a CA from the Glagov phenomenon, the mild dilatation of the outer diameter of a coronary artery seen in early atherosclerotic degenerative disease. According to the Glagov theory, the outer diameter of the coronary arteries dilates in the early phases of atherosclerosis, when plaque deposition leads to positive remodeling with preservation of the vessel lumen.[4] Such positive remodeling probably does not allow for a dilatation of the coronary artery >50% of the previous normal diameter.

Studies of coronary flow velocity, by flow or Doppler wires, interrogating the full cross- sectional aneurysmatic area of a given CA, would give the most accurate diagnosis of a the severity of a CA. Coronary flow velocity studies would be most capable of generating the precise indication of the degree of dilatation based on the principle that blood flow velocity indices at dilated arterial segments (more at the periphery than at the center) are inversely related to segmental dilatation size.[5] Normal coronary size and blood flow velocity are related the size of the dependent myocardial territory and its metabolic needs during rest and exercise.[2]

The current article by Daniels and colleagues[6] in this issue of *Circulation* implies such methodological difficulties in identifying Kawasaki disease-related CA, as suggested by the fact that the study includes only adult patients who are <40 years of age (older patients would have a higher probability of atherosclerotic dilatation, presumably); indeed, the majority of suspected cases of Kawasaki disease (KD) in this article had aneurysmal diameters >100% larger than the reference diameter (hence, larger than is justifiable by the Glagov phenomenon). Unfortunately, the reference diameters were not reported. Coronary aneurysms are frequently encountered during acute KD (≈50% of cases)[1,7–9] and years after acute KD (when the incidence of CA is about 25% in untreated KD and 5% in KD treated with γ globulin).[1,7–9] Coronary aneurysm constitutes a fundamental hallmark for the clinical diagnosis of prior KD arteriopathy. In Figures 1 and 2, angiographic and intravascular ultrasound imaging show an example of this pathology, featuring typical absence of significant intimal atherosclerotic thickening in the coronary segments proximal and distal to the aneurysms, as apparent in this 35-year-old patient, who had KD when she was 5 years of age. Also shown is evidence of perivascular fibrosis but no calcifications outside the CA (Figure 2). Given the persistent limitations in the reliability of clinical and arteriographic diagnosis of KD, the important question is whether such a diagnosis must be established in an adult with CA or whether the size of a CA alone is an adequate criterion for determining a prognosis and identifying the ideal treatment in a given patient. The only circumstance in which a causal diagnosis could be clinically valuable would be if it were important to detect or treat residual inflammatory activity. However, neither a long-term infection-based cause nor evidence of a persistent long-term inflammatory state has been validated in adult patients.[1,5,7–12]

Recently, experimental animal models of an arteritis similar to KD have been developed, and they suggest the possibility that KD is not a specific entity but rather the result of a systemic, yet primarily coronary, arteritis that originates in response to different environmental insults, modulated on the basis of variable genetic backgrounds, and eventually leading to a wide spectrum of clinical presentations.[10,11] This is also supported by the preliminary finding that, in mice-based experimental arteritis, gamma globulin also has a protective effect against the development of CA, as in clinical KD.[14] Recent mechanistic studies suggest that the initial inflammatory reaction in KD is mediated by the early invasion of the intima and media by granulocytes and T cells

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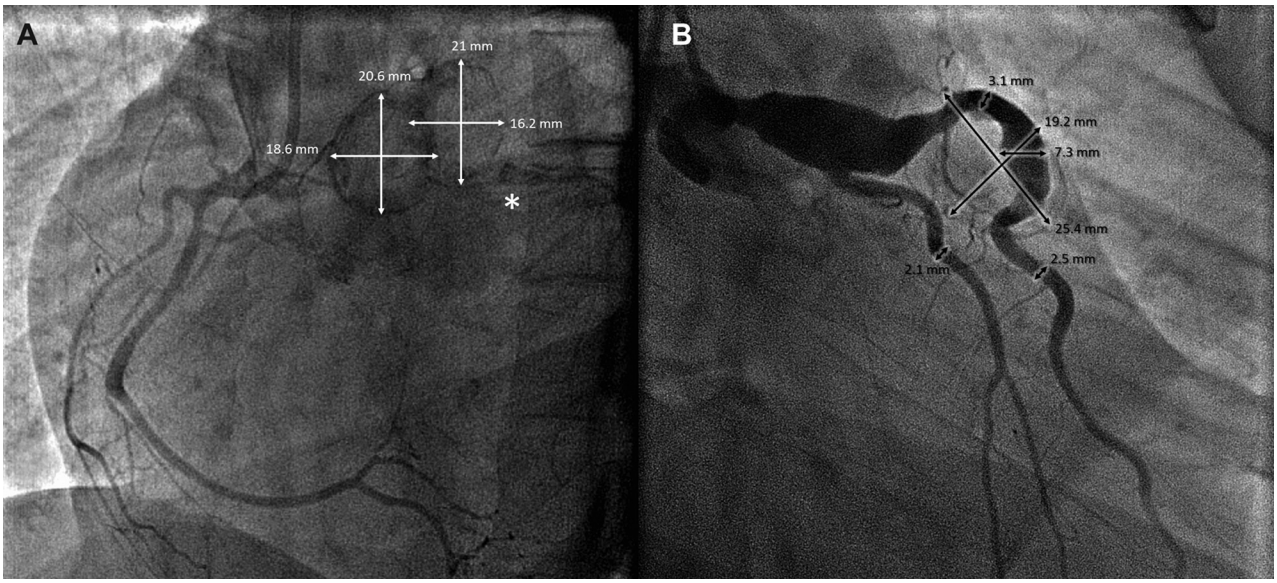

Figure 1. Catheter coronary angiography still frames in a 35-year-old patient with Kawasaki-proven aneurysms. In **A**, the right coronary artery is free of significant angiographic disease, whereas the localized heavy calcifications in the left coronary arteries are typical of coronary Kawasaki-related aneurysms. During coronary angiography, such calcifications (located on the outer arterial wall) allow for the measurement of the outer diameters of the left coronary aneurysms (**A**), whereas mural thrombosis can be assessed (as indicated by the space between the angiographic lumen in **A** and the outer calcifications in **B**). Measurements of inner and outer diameters are provided in mm. Notice the relatively normal lumens at the patent branches distal to the aneurysms, whereas the circumflex (asterisk) and the diagonal branches were chronically occluded at their origins from the aneurysmatic proximal segments.

in the presence of systemic leukocytosis.[1,8,9,11–13] During the early inflammatory stage, lymphocytes, plasma cells, and macrophages invade the arterial wall, expressing cytokines like tumor growth factor, platelet-derived growth factor A, basic fibroblast growth factor, tumor necrosis factor α, and vascular endothelial growth factor.[1,8,9,11,12] In particular, the experimental model of arteritis in mice has been shown to be accompanied by T cell activation, tumor necrosis factor production, and matrix metalloproteinase-9 expression in the arterial wall at the early phase of activity.[14] Such intense inflammatory response is generally absent in the chronic phase of KD in adults.[8,9,11]

The prognosis of a CA in adults is related to demonstrable features in any given case: the location of the CA (prognosis is usually worse when the CA is proximal), the size of the CA (CAs of 8 mm in diameter are associated with a worse prognosis, as Daniels and colleagues[6] write), whether the CA is expanding, the presence of mural thrombosis, and a history of distal coronary embolism. A discussion of differential causal diagnosis could be aimed at ruling out either other kinds of arteriopathies (those with similarly unclear pathogeneses), like Behçet disease and Takayasu arteritis, or other conditions that could be persistently active, such as autoimmune diseases, or inactive, such as posttraumatic (including surgical) cases. All are treated like CA in KD unless indices of inflammatory activity are present.

In KD, CAs in adults are generally biologically stable in that there is no inflammatory activity, even though they are subject to progressive calcifications located at the media/intimal interface or the subendothelial surface.[3,9] The prognosis is largely determined by the increased tendency toward mural thrombosis and embolization, which is implied by coronary dilatation and its consequent slow runoff, especially in the presence of a damaged endothelial/intimal lining. The

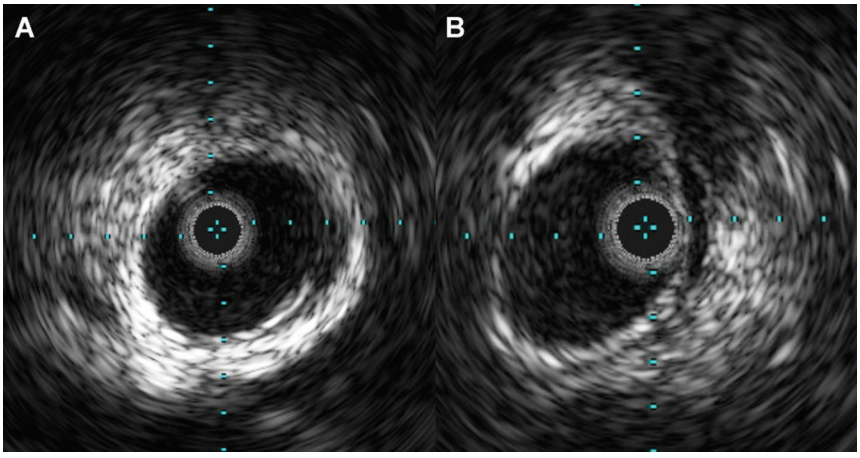

Figure 2. A, Intravascular ultrasound imaging of the left main ostium. Note the absence of intimal thickening and the presence of extensive perivascular fibrosis in the absence of aneurysm (just proximal to large aneurysm of the same vessel). Space markings are in mm. **B**, Intravascular ultrasound imaging of the LAD, distal to the aneurysm. Note the absence of intimal thickening and of calcium deposits. Moderate amount of perivascular fibrosis is present.

risk of coronary external wall rupture is remote and limited to cases with CA diameters >20 mm or that grow with time.[1,7–9]

As Gordon and colleagues[12] state in their recent review of KD, "treatment regimens should be tailored based on the size of the aneurysm," and complementary treatment options in adult patients include antithrombic medication and platelets aggregation inhibitors therapy, surgery, and angioplasty.[7,8] Interestingly, Kawasaki-related CA (K-CA) apparently does not cause an increased incidence of lipid deposition in young adults with KD[8–12] (Figures 1 and 2), but no prospective studies of significant size have been done in older patients, which is currently becoming a growing population. The finding of intense perivascular fibrosis on intravascular ultrasound could be considered to suggest a protective effect, possibly mediated by the induced absence of periarterial fat deposits implied by the observed absence of even the mild atherosclerotic intimal thickening that would be expected of a patient similar in age to the one in Figures 1 and 2.

The potential for KD to develop coronary stenoses associated with CAs apparently has 2 main causes: first, the proliferative mechanism intrinsic to the acute KD process, which causes vascular media–originated smooth muscle cells to proliferate and migrate from the damaged media into the intimal layer, producing large amounts of extracellular matrix and forming a hard fibrotic scar[9]; and second, mural thrombosis/embolism.

Often difficult to diagnose, local coronary embolism can cause chest pain and acute myocardial infarction in patients with K-CA. MRI with a scar protocol is the most precise method currently available to identify necrotic damage from local coronary embolisms.

Coronary aneurysms may be progressive in size for a few different reasons. The original disruption of the media, which is the strongest structure in the arterial wall, is the main causative factor. In theory, it is possible that exercise habits could contribute to the expansion of CA, especially in younger patients. Heavy weightlifting in particular should probably be avoided because of the sudden increase in intravascular pressure and strain that accompany it. Hypertension and trauma by sudden deceleration could also be contributing factors.

Research on the development of K-CA should focus on prospective studies of pediatric patients known to have had KD[10,11] rather than prevalence studies of general adult populations; such studies would lack clear inclusion criteria. The pretest likelihood of KD and CA should be known (reasons for study), and the diagnostic methods (autopsy, computerized axial tomographic scan, or coronary angiography) to be used should be selected, with the intention to obtain interpretable information.

In conclusion, ascertainment of a past history of KD as the pathogenesis of CA in the adult is frequently difficult and only marginally helpful in planning optimal therapy; rather, treatment should be based on CA architecture and pathophysiology. In contrast, in children, the diagnosis of acute KD is essential to establish prevalence data and, most importantly, to institute early treatment with intravenous gamma globulin to prevent aneurysm formation.[1,7–9,14]

Disclosures

None.

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