Coronary Artery Aneurysm
A Review and Hypothesis Regarding Etiology

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Context.—Coronary artery aneurysm is an uncommon condition that can be a cause of death when it thromboses or ruptures. It is always associated with destruction of the tunica media, usually associated with atherosclerosis, and commonly associated with chronic inflammation.

Objective.—To review the pathology, epidemiologic and clinical features, and pathophysiology of coronary artery aneurysm, particularly new research results, drawing out implications for the understanding, diagnosis, and treatment of this condition.

Data Sources.—Pertinent literature and illustrative cases at our institution.

Conclusions.—Inflammation spilling over into the tunica media from the tunica intima may link atherosclerosis to aneurysm formation, but vasculitis without atherosclerosis causes coronary artery aneurysms in young children with Kawasaki disease. Increased proteolysis of extracellular matrix proteins is probably one mechanism of coronary artery aneurysm formation, either due to overactive matrix metalloproteinases or underactive inhibition of these proteinases, and an excess of transforming growth factor β may be another mechanism in the pathogenesis. Coronary atherosclerosis is a universal disease of adults, but only 1.5% of them have coronary aneurysms; this small group may be those with a second coronary artery disease, such as vasculitis.

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Coronary artery aneurysm is an uncommon condition that may commonly represent the result of vasculitis, excess active transforming growth factor β (TGF-β) or dysregulation of matrix metalloproteinases. This is not the conclusion of any one specific study, meta-analysis, or previous review, but rather the hypothesis that our experience and review led us to. When encountered at autopsy, coronary artery aneurysm may represent the intermediate cause of death because abnormal blood flow within the aneurysm may lead to thrombus formation, occlusion, embolization, myocardial ischemia, or myocardial infarction. Coronary artery aneurysm is a neglected topic in the pathology literature, with contributions limited primarily to reports of single cases. In this review, we summarize the gross and microscopic pathology of coronary artery aneurysms, the epidemiologic and clinical features of the condition, and some thoughts about the pathogenesis and treatment.

GROSS AND MICROSCOPIC FEATURES

An aneurysm is an abnormal localized outpouching of a blood vessel (or the heart). An aneurysm of an artery is commonly defined as a localized dilatation exceeding the diameter of adjacent normal segments by 50%.1 Giant coronary artery aneurysms are those more than 4 cm in diameter.2 A true arterial aneurysm can be fusiform, involving the full circumference of the blood vessel, or saccular, involving only a portion of the circumference. Fusiform aneurysms are much more common than saccular aneurysms. A false aneurysm or pseudoaneurysm is actually a rupture of the artery contained by the tunica adventitia or a blood clot.

The histopathology of coronary artery aneurysms was described in 9 of the 10 cases from a series of 694 autopsies performed from 1955 to 1957 in Albany, NY3 and in 52 cases from the Armed Forces Institute of Pathology and a veterans’ hospital.4 All coronary aneurysms 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, an inflammatory reaction, and sometimes hemorrhages can be seen, sometimes limited to the tunica intima with atherosclerosis, sometimes extending into the tunica media and sometimes into the indistinct border zone. The inflammatory reaction consists chiefly of lymphocytes, but includes macrophages, sometimes with 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 sometimes transmural, involving all 3 layers of the artery. Thrombus formation is in-
Figure 1. Gross pathology of 1.5-cm left circumflex coronary artery aneurysm.

Figure 2. Histology of the left circumflex coronary artery aneurysm. A, Tunica intima expanded by atherosclerosis (left) and tunica media attenuated and densely infiltrated by inflammatory cells (right) (hematoxylin-eosin, original magnification ×10). B, Higher power showing the inflammatory cells to be predominantly lymphocytes, with a few residual smooth muscle cells (bottom center) (hematoxylin-eosin, original magnification ×20). C, Verhoeff van Gieson stain showing only wisps of black elastin in the attenuated tunica media (original magnification ×10). D, Immunostain for smooth muscle actin showing markedly decreased staining transitioning to totally absent staining (center, left to right), representing the loss of smooth muscle in the tunica media (original magnification ×10).

Coronary Artery Aneurysm: Nichols et al

Figure 1 shows the gross pathology of a coronary artery aneurysm discovered at autopsy in a 52-year-old man with a history of obesity, hypertension, and hyperlipidemia, but not coronary artery disease, who collapsed and died at his home in front of his wife. The autopsy showed an aneurysm of the left circumflex coronary artery, 1.5 cm in diameter, with occlusive recent thrombosis; an aneurysm of the right coronary artery, 0.6 cm in diameter; an abdominal aortic aneurysm, 4 cm in diameter; 3 iliac artery aneurysms; and old and subacute myocardial infarctions. Histological evaluation revealed severe cystic medial degeneration and lymphohistiocytic inflammation with giant cells in the tunica media. Cystic medial degeneration was not seen outside of the areas of inflammation and aneurysm. Figure 2 illustrates the microscopic pathology of the large coronary artery aneurysm. Postmortem examination in this case also showed evidence of healed vasculitis in the kidneys and granulomatous inflammation in the spleen. Verhoeff van Gieson stain showed extreme fragmentation and loss of elastic fibers in the tunica media of the left circumflex coronary artery aneurysm and right...
coronary artery aneurysm. Immunostain for smooth muscle actin showed a large area of loss of smooth muscle cells in the left circumflex coronary artery aneurysm. The inflammation was transmural and segmental. The loss of smooth muscle cells showed a sharp border with the adjacent normal portion of artery.

Figure 3 shows the gross pathology of a coronary artery aneurysm discovered at autopsy in an 18-month-old boy with fever and skin rash for 2 weeks, diagnosed as scarlet fever and treated with penicillin, who died suddenly and unexpectedly. The autopsy showed a large aneurysm of the right coronary artery, distended with thrombosis. Figure 4 illustrates the microscopic pathology. In addition to the recent and fresh occlusive thrombosis, the artery showed transmural inflammation, primarily with lymphocytes, but including macrophages, plasma cells, and a few eosinophils and neutrophils.

**Epidemiologic and Clinical Features**

Two very different kinds of studies suggest that the incidence of coronary artery aneurysms is 1.4%, one based on 7101 coronary angiographies in Germany and the other based on 694 autopsies in the United States. The incidence was 1.5% in a Russian autopsy series of 1000 hearts with atherosclerosis. There are no doubt important genetic and possibly environmental influences on the incidence because it is lower in Asia than in North America and Europe. In India, in a series of 3200 coronary angiograms, 22 patients (0.7%) had saccular aneurysms. In Taiwan, in a series of 10 120 coronary angiograms, 12 patients (0.1%) had saccular or fusiform aneurysms. In contrast, in patients with Kawasaki disease, a study of 302 patients from the US Children’s National Medical Center found a 10.3% incidence of coronary aneurysms in patients of Asian ethnicity, compared with 6.9% in those of Caucasian ethnicity and 1.2% in those of African ethnicity. One study of 20 087 coronary angiographies found an incidence of 4.9%, and another study of 3900 coronary angiographies found an incidence of 5.3%, but both studies counted ectasia, which is a generalized dilatation of a blood vessel, as aneurysm, greatly inflating the incidence. A disparate study of 32 372 coronary angiographies found an incidence of 0.9%, but this study counted only aneurysms equal to or greater than twice the diameter of the adjacent normal artery (or equal to or greater than 0.8 cm) as aneurysms. One could imagine that the incidence found in coronary angiographic studies might be falsely low if luminal thrombi obscured the full diameter of aneurysms, but an intravascular ultrasound study of angiographic coronary artery aneurysms found that many of them were actually normal arterial segments adjacent to stenoses, suggesting that angiographic studies likely yield falsely high incidences.

Coronary artery aneurysms are more common in men. They were present in 1.79% of the 4970 men and 0.56% of the 2131 women in an angiographic study. Nine of the 10 coronary artery aneurysms in an autopsy study were men, and 57 (72%) of the 79 cases reported in the medical literature between 1812 and 1960 were in men. All 15 cases in another autopsy study were male. Coronary artery aneurysms are most commonly diagnosed in late middle-aged patients. The average age at angiographic diagnosis in one study was 63.5 years. The average at autopsy diagnosis was 54.4 years in one study and 65.9 years in another study. Patients with coronary artery aneurysms commonly present with angina pectoris, dyspnea, edema, or sudden death, but it is difficult to say whether these are manifestations (signs and symptoms) of the coronary artery aneurysms or of the usually accompanying coronary atherosclerosis, coronary thrombosis, coronary stenosis, coronary vasculitis, acute myocardial infarctions, or old myocardial infarctions.

Coronary artery aneurysms are associated with aortic aneurysms. In a prospective study of 61 patients with coronary aneurysms detected angiographically, 18 (30%) had abdominal aortic aneurysms, compared with 3 (5%) of 61 controls. The combination of coronary, aortic, and iliac aneurysms in a 51-year-old man with hypertension and elevated C-reactive protein and erythrocyte sedimentation rate, similar to the case illustrated in Figures 1 and 2, has been reported. Coronary artery aneurysms are occasionally reported in association with cerebral artery aneurysms. Cerebral artery aneurysms are more common in patients with polycystic kidney disease and, as one might suspect from this, coronary artery aneurysms are associated with polycystic kidney disease. Coronary arterial aneurysms are also associated with venous diseases featuring abnormal dilatation: varicose veins and varicoceles.

Hypertension is associated with aortic and cerebral artery aneurysms, so one might expect an association between hypertension and coronary artery aneurysms. In the study of 7101 coronary angiographies in Germany, 75% of patients with aneurysms had hypertension, compared with 66.7% of patients with stenotic coronary artery disease without aneurysms, but this difference was not statistically significant (P = .30). A study of 3900 coro-
Coronary angiographies in Greece found a 32.5% rate of hypertension among patients with stenotic and aneurysmal coronary artery disease, a 35.5% rate among patients with aneurysmal but no stenotic disease, and a 35.1% rate among patients with stenotic but no aneurysmal disease, which was not statistically significant. A study of 32,372 coronary angiographies in the United States found that 61% of aneurysmal patients had hypertension, compared with 55% of controls, but the difference was not statistically significant ($P = .13$). The autopsy study of 52 patients found that 13 (33%) of the 39 for whom sufficient clinical history was available had hypertension, including 52% of those with aneurysms attributed to atherosclerosis and none of those with aneurysms attributed to inflammation, but there was no control group. Overall, a review of the evidence suggests that there is no significant association between hypertension and coronary artery aneurysms.

Multiple studies suggest that the prognosis of patients with coronary artery aneurysms associated with coronary atherosclerosis is not different than the prognosis of patients with coronary atherosclerosis without aneurysms. One study included 31 coronary aneurysm patients who did not have coronary atherosclerosis, and they had a better prognosis, with no myocardial infarctions or cardiac deaths after 2 years, compared with the 4.9% incidence among the 172 patients who had a combination of coronary atherosclerosis and coronary aneurysm. Another study, however, found a 56% higher mortality rate over 5 years of the 276 patients with aneurysms among 32,372 angiography patients, but this was the study that counted only larger aneurysms. The higher mortality of patients with larger aneurysms suggests that there may be a threshold in size above which the prognosis is poorer. In fact, consistent with this concept, the literature is replete with case reports of mortality due to giant coronary aneurysms.

**PATHOGENESIS AND TREATMENT**

Causes of coronary artery aneurysms are said to include atherosclerosis (accounting for 50% of cases), Kawasaki disease, polyarteritis nodosa, systemic lupus erythematosus, infection, trauma, dissection, angioplasty, and congenital malformation. Behcet disease is also a cause of atherosclerosis. One study included 31 coronary aneurysm patients who did not have coronary atherosclerosis, and they had a better prognosis, with no myocardial infarctions or cardiac deaths after 2 years, compared with the 4.9% incidence among the 172 patients who had a combination of coronary atherosclerosis and coronary aneurysm. Another study, however, found a 56% higher mortality rate over 5 years of the 276 patients with aneurysms among 32,372 angiography patients, but this was the study that counted only larger aneurysms. The higher mortality of patients with larger aneurysms suggests that there may be a threshold in size above which the prognosis is poorer. In fact, consistent with this concept, the literature is replete with case reports of mortality due to giant coronary aneurysms.

Systemic lupus erythematosus commonly causes arteritis; this disease is most common in black women of childbearing age, and coronary aneurysms have been reported as a manifestation of systemic lupus erythematosus. Takayasu arteritis commonly involves the aorta and its major thoracic branches and features giant cells; this is primarily a disease of young Asian females. Coronary angiograms of 81 patients with Takayasu arteritis showed dilatation in 4, but diffuse dilatation perhaps better characterized as ectasia. Giant cell arteritis is not reported as a cause of coronary artery aneurysms, but this is primarily a disease of elderly white women who all have coronary arterosclerosis, so inflammation of the coronary arteries in such patients is no doubt interpreted as part of the arterosclerotic disease. The study of 52 cases of coronary artery aneurysms at autopsy included 14 patients with no coronary arterosclerosis (6 with Kawasaki disease, 1 each with granulomatous, mycotic, rheumatic, and syphilitic arteritis, and 4 without evident cause).

Coronary artery aneurysms may be caused by hypersensitivity vasculitis caused by drug-eluting stents. Coronary artery aneurysms have been increasingly reported as a complication of drug-eluting stenting. Aneurysm formation is a recognized complication of coronary artery stenting with bare metal stents and of angioplasty without stenting. To some extent, these aneurysms presumably present in coronary artery aneurysms are merely reacting to cholesterol from atheroma and erythrocyte breakdown in the adjacent tunica intima, that the lymphohistiocytic inflammation is merely spillover from the atherosclerosis in the adjacent tunica media, and that cystic medial degeneration and aneurysm formation are merely side effects of this spillover inflammation. Alternatively, one could hypothesize that the inflammation is sometimes due to autoimmune vasculitis coexisting with the atherosclerosis.

Increased proteolysis of extracellular matrix proteins is probably a mechanism of coronary artery aneurysm formation. Matrix metalloproteinase 1 (interstitial collagenase), matrix metalloproteinase 2 (gelatinase A), matrix metalloproteinase 3 (stromelysin 1), matrix metalloproteinase 9 (gelatinase B), and matrix metalloproteinase 12 (macrophage metalloelastase) are capable of degrading essentially all components of arterial wall matrix (elastin, collagen, proteoglycans, laminin, fibronectin, etc) and are present in elevated concentration in aortic aneurysms, while there are decreased levels of tissue inhibitors of matrix metalloproteinases. The matrix metalloproteinase 3 5A allele is associated with higher promoter activity for transcription of the gene, and this allele is more common in patients with coronary artery aneurysms plus atherosclerosis than patients with only coronary atherosclerosis. In patients with Kawasaki disease, those with coronary artery lesions have higher plasma levels of both matrix metalloproteinase 3 and matrix metalloproteinase 9. Vasculitis can cause aneurysms without atherosclerosis. This is most obvious in Kawasaki disease, which commonly involves the coronary arteries and commonly causes aneurysms of the coronary arteries. This is primarily a disease of young children, with a peak incidence at around 1 year of age. Various other forms of vasculitis can involve the coronary arteries in different types of patients. Polyarteritis nodosa is primarily a disease of middle-aged men and commonly causes aneurysms. Coronary aneurysms occur in 9% of patients with polyarteritis nodosa. Systemic lupus erythematosus commonly causes arteritis; this disease is most common in black women of childbearing age, and coronary aneurysms have been reported as a manifestation of systemic lupus erythematosus. Takayasu arteritis commonly involves the aorta and its major thoracic branches and features giant cells; this is primarily a disease of young Asian females. Coronary angiograms of 81 patients with Takayasu arteritis showed dilatation in 4, but diffuse dilatation perhaps better characterized as ectasia. Giant cell arteritis is not reported as a cause of coronary artery aneurysms, but this is primarily a disease of elderly white women who all have coronary arterosclerosis, so inflammation of the coronary arteries in such patients is no doubt interpreted as part of the arterosclerotic disease. The study of 52 cases of coronary artery aneurysms at autopsy included 14 patients with no coronary arterosclerosis (6 with Kawasaki disease, 1 each with granulomatous, mycotic, rheumatic, and syphilitic arteritis, and 4 without evident cause).
reflected dilatation of the diseased artery by stretching of the wall due to inflation of the angioplasty balloon as a simple mechanical consequence of the procedure. That is, however, an unlikely explanation for aneurysms developing months to years after drug-eluting stent placement. The drugs in these stents are immunosuppressants such as sirolimus, which inhibit inflammation, or chemotherapeutic agents such as paclitaxel, which inhibit cell proliferation and, in turn, inflammation. As long as the drug is eluting, hypersensitivity vasculitis is presumably inhibited, but once all the drug has eluted, the polymer in which the drug is embedded may elicit a hypersensitivity reaction uninhibited by the drug. This concept is supported by the finding of an eosinophilic infiltrate in the few cases of such poststen ost coronary artery aneurysms examined histologically.\textsuperscript{36,37}

Connective tissue diseases such as Marfan syndrome can cause aneurysms without atherosclerosis. Marfan syndrome is associated with mutations in the gene for fibrillin (a major component of microfibrils associated with elastin fibers), and fibrillin is homologous with the family of latent TGF-β binding proteins, which hold TGF-β in an inactive complex.\textsuperscript{38} Other aneurysm syndromes have recently been elucidated to involve mutations in the receptors for TGF-β, suggesting that the pathogenesis of aneurysm formation in all these syndromes is mediated by an excess of active TGF-β.\textsuperscript{39} Cystic medial degeneration is commonly a feature of the aneurysms in Marfan syndrome, so its presence in a coronary artery aneurysm may be indicative of a congenital genetic defect causing an excess of active TGF-β. Cystic medial degeneration is also, however, commonly seen in the aortic aneurysms of late middle-aged and elderly patients without Marfan syndrome,\textsuperscript{40} but it could be indicative of an excess of active TGF-β in them as well. Cocaine may also cause coronary artery aneurysms by inducing an excess of active TGF-β.\textsuperscript{41}

The pathogenesis has implications for treatment. 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.\textsuperscript{42} Perhaps such drugs could prevent coronary aneurysms as well. The secretion of metalloproteinases 1, 2, 3, and 9 from macrophages and vascular smooth muscle cells can be inhibited by the statins (hydroxymethylglutaryl coenzyme A reductase inhibitors) simvastatin, lovastatin, and cerivastatin.\textsuperscript{43} This suggests the possibility that these drugs may have value in inhibiting the tunica media destruction characteristic of coronary artery aneurysms. Given the frequency of thrombosis in coronary artery aneurysms, antplatelet therapy (with aspirin or clopidogrel) or anticoagulation (with warfarin) has predictably been reported useful in the medical management of these aneurysms.\textsuperscript{44,45} Stenting and coil embolization have been used in the nonsurgical management of coronary aneurysms.\textsuperscript{46,47} Some surgeons believe that surgical repair is mandatory when a coronary aneurysm is 3 times larger than the original vessel diameter.\textsuperscript{48} Nonsurgical management, however, of a giant (7-cm-diameter) coronary artery aneurysm during a 2-year period has been reported.\textsuperscript{49} Needless to say, coronary artery aneurysm is too uncommon a condition for large randomized clinical trials comparing different therapies, so opinions about the optimum management must be based on personal experience and reports of single cases and small series.

CONCLUSIONS

Coronary artery aneurysms are usually associated with atherosclerosis and commonly thought to be caused by atherosclerosis, but they may represent the superimposition of autoimmune vasculitis. In some cases, however, the atherosclerosis may be superimposed on pre-existing aneurysms from Kawasaki disease in childhood. In still other cases, the atherosclerosis may cause aneurysms only when patients have polymorphisms leaving them with a baseline defect in the mechanisms of vascular remodeling. These genetic defects include excess active TGF-β, dysfunctional TGF-β binding proteins, overactive matrix metalloproteinases, or loss of function mutations in inhibitors of matrix metalloproteinases. Atherosclerosis is a universal disease of the coronary arteries of adults, but only 1.5% of them have aneurysms, and this small group may be those genetically susceptible to a second hit in a two-hit process resulting in aneurysm.

References


