Etiology of Aortic Aneurysm

CHRISTOPHER K. ZARINS, M.D., F.A.C.S.
CHIDESTER PROFESSOR OF SURGERY
CHIEF, DIVISION OF VASCULAR SURGERY
STANFORD UNIVERSITY SCHOOL OF MEDICINE
STANFORD, CALIFORNIA

RAMIN E. BEYGUI, M.D.
FELLOW, DIVISION OF VASCULAR SURGERY
STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA

In the past three decades, the prevalence of aortic aneurysms has increased threefold. Incidence of aortic aneurysms increases with age and as the population ages, the prevalence increases. Population-based studies have shown that 10% of men over the age of 70 have abdominal aortic aneurysms. After many years of research, the exact pathogenesis of degenerative aneurysms—the most common form of aneurysm—is still unknown, although a number of factors including genetic, protelytic enzymes, hemodynamics, inflammation, and infection have been implicated.

GENETIC FACTORS

Since the report by Clifton[1] of three brothers with ruptured aortic aneurysms, a number of investigators have studied and reported a genetic predisposition to aortic aneurysms.[2-5] Marfan's syndrome, an autosomal dominant trait, is related to a gene mutation on the long arm of chromosome 15. This gene codes the micofibrillar protein fibrillin. The point mutation results in placement of arginine by glycine.[6] The result is weakening of the aortic wall and predisposition to dissections and aneurysms. Cystic medial necrosis, as described by Erdheim, is an accumulation of basophilic amorphous material in the media with formation of cystic mucoid pools. Specificity of this medial lesion is still controversial. This lesion has a variable presence in aortic dissection and diffuse aneurysms of the aorta in patients with or without Marfan's genotype.

Menkes' kinky-hair syndrome is attributable to a mutation linked to the X chromosome. This mutation results in a defective copper transport mechanism.[7] Lack of copper results in abnormal cross-linking of collagen and elastin, rendering the tissue matrix unstable. The arterial manifestations of this syndrome are intracranial berry aneurysms and peripheral arterial aneurysms.[8]

Ehler-Danlos syndrome (type-IV) is clinically manifested by cutis laxa (hyperelasticity of skin), articular hypermobility, and fragile blood vessels. Ehler-Danlos syndrome has been divided into nine subtypes. The most common inheritance pattern is autosomal dominant. Uncommonly, X-linked and autosomal recessive forms of transmission have been encountered. In Ehler-Danlos syndrome type-IV (vascular type), the defect appears to affect cross-linking of type III collagen fibrils. Blood vessel walls are weak and susceptible to aneurysm formation and rupture.[9]

PROTEOLYTIC ENZYMES

Destruction of the arterial wall matrix and degradation of collagen has been implicated in the pathogenesis of aneurysms and has been under investigation for a decade. Recently, investigation by Irizarry and coworkers demonstrated the presence of interstitial collagenase known as matrix metalloproteinase-1 (MMP-1) in specimens of abdominal aortic aneurysms.[10] In this report, control aortic extracts demonstrated only low levels of detectable MMP-1 by the immunoblot technique. Newman and associates,[11] using a recombinant tissue inhibitor of metalloproteinase-1, isolated collagenase (MMP-1) and stromelysin-1 (MMP-3) from abdominal aortic aneurysm tissue. Using fluorescence-activated cell counting, they found a fiftyfold increase in proteolytic activity in macrophages and increased activity in lymphocytes. This study identified mononuclear cell infiltrates (macrophages and

lymphocytes) as possible sources of proteolytic enzymes in aortic aneurysms. Comparative immunoblotting of specimens obtained from 10 abdominal aortic aneurysms demonstrated activated forms of MMP-9 and MMP-3 whereas only trace amounts of these enzymes were identified in the six control aortas.[12] This study supported the hypothesis that proteolytic enzymes play a significant role in destruction of aortic matrix and formation of aneurysms. Furthermore, using immunohistochemical techniques, Newman and colleagues localized MMP-3 (stromelysin-1) and urokinase-like plasminogen activator (uPA) to macrophage-like mononuclear cells that are infiltrating the aortic wall.[13] In the same study, MMP-1 (interstitial collagenase) was localized in the mesenchymal cells of the aneurysmal aortic wall. Thus, it was suggested that macrophages play a role in activation of matrix protein destruction and pathogenesis of aneurysms.

In order to elucidate the role of these proteolytic enzymes in occlusive disease versus aneurysmal disease, McMillan and coworkers analyzed aortic tissue obtained from aneurysmal, occlusive, and normal aortas.[14] Analysis of mRNA using the Northern blot technique was performed. MMP-2 and tissue inhibitor of metalloproteinase type two (TIMP-2) were expressed in aneurysmal, occlusive, and normal aortas. MMP-2 expression, however, was significantly higher in aneurysmal aortas when compared to occlusive or normal specimens. The cultured vascular smooth muscle cells expressed both MMP-2 and TIMP-2 when obtained from aneurysmal aortas. The authors proposed a possible role for MMP-2 in plaque remodeling in occlusive disease and in matrix degradation of aneurysmal disease. Freestone and coworkers compared small aneurysms (4 to 5.5 cm) to larger aneurysms, using zymography and immunoblotting techniques and showed higher concentration of MMP-2 (gelatinase A) in small aneurysms compared to larger aneurysms and normal aortas.[15] MMP-2 was concentrated along the acellular bands of the media and plaques. MMP-9 (gelatinase B), on the other hand, was highest in concentration in larger aneurysms and was localized to the inflammatory cells of the adventitia. This study also proposed a role for MMP-2 in the remodeling of atherosclerotic plaques and for MMP-9 in enlargement and rupture of aneurysms.

The discovery of genetic factors and the recognition of proteolytic enzyme activity suggests a potential role for pharmacologic intervention in treatment of degenerative aneurysms. Drugs which inhibit protease activity or those which alter inflammation or metabolism of vascular matrix may have potential as treatments for aneurysmal disease.

HEMODYNAMIC INFLUENCE

Shear stress in arteries is directly proportional to velocity of flow and blood viscosity and inversely proportional to the cube of the lumen radius. Increases in blood flow stimulate compensatory arterial enlargement which results in normalization of wall shear stress. Arterial enlargement in response to shear stress may be mediated by nitric oxide. Nitric oxide is produced by conversion of L-arginine to citruline which is regulated by nitric oxide synthase (NOS). Nitric oxide elaborated by the endothelial cells is a potent vasodilator and a modulator of arterial enlargement.[16] Lower shear stress in dilated vessels may result in deposition of atherosclerotic plaques, as has been demonstrated in the carotid sinus.[17,18] The observation that abdominal aortic aneurysms are more prevalent in World War II amputees than in non-amputee veterans also supports the hypothesis that hemodynamic factors are important in the pathogenesis of aneurysms.

ATHEROSCLEROSIS

Atherosclerosis is a complex and dynamic process involving various stages of plaque formation, compensatory enlargement, media thinning and degradation, and plaque evolution.[18] Arterial enlargement is a prominent feature of atherosclerosis and may play a role in the pathogenesis of aneurysm. This compensatory mechanism may be mediated by nitric oxide produced by the endothelial cells. *Plaque formation* is usually eccentric with respect to longitudinal axis of the blood vessel, leaving a round luminal contour and a plaque surface covered by a fibrous cap. Plaque formation most often does not result in luminal stenosis due to compensatory arterial enlargement. *Arterial enlargement* has been documented in relation to atherosclerosis in various arteries including the aorta, particularly the abdominal aorta which is vulnerable to aneurysms. Plaque formation in the abdominal aorta is usually accompanied by *media thinning*, atrophy, and loss of lamella architecture. As previously discussed, matrix metalloproteinases are found to be concentrated along the acellular bands of the media as well as in relation to plaques leading to matrix degeneration and aneurysmal enlargement.

SYSTEMIC INFLAMMATORY DISEASE

A number of systemic inflammatory diseases (Takayasu's disease, giant cell arteritis, systemic lupus erythematosus, polyarteritis nodosa, Behçet's disease, and Kawasaki's disease) are associated with aortic aneurysms. Inflammatory cells may play an important role in the pathogenesis of aneurysms through proteolytic enzyme release, as already discussed. In light of recent evidence of localization of matrix metalloproteinases in mononuclear inflammatory cells of the adventitia of aortic aneurysms, a similar etiology may be suspected in aneurysms associated with systemic inflammatory and autoimmune diseases. Beckman and coworkers showed the presence of inflammatory infiltrates in two-thirds of abdominal aortic aneurysms. Inflammatory aneurysms not associated with systemic disease account for 2% to 5% of abdominal aortic aneurysms. It is well known that pain and inflammation associated with inflammatory aneurysms disappear promptly after open aneurysm repair. Chuter has also reported a decrease in the diameter and thickness after treatment by endoluminal stent-grafts, suggesting that hemodynamic forces such as arterial blood pressure and pulsation may promote inflammation and aneurysm formation.[19]

INFECTIOUS ANEURYSMS

Prior to the availability of antibiotics, syphilitic aneurysms, which predominantly involve the proximal thoracic aorta, accounted for the majority of infectious aneurysms. Pathologic examination of syphilitic aneurysms revealed an inflammatory reaction in the adventitia and vasa vasorum with a mononuclear infiltrate. Today Salmonella species remain the most common gram-negative organisms and Staphylococcus and Streptococcus species are the most common gram-positive organisms isolated from infectious aneurysms. Opportunistic organisms such as fungi and mycobacteria are found in infectious aneurysms of immunocompromised patients.[20] Ernst and colleagues reported a 10% incidence of positive cultures obtained at the time of routine aneurysm repair.[21] Therefore, colonization

of perivascular tissue occurs more often than invasive infection of arterial aneurysms. It is suggested that inflammation caused by infection is implicated in the pathogenesis of certain aneurysms. Preexisting aneurysms may become secondarily infected during a bacteremic period. These cases are distinguished from those in which infection and inflammation cause aortic aneurysm formation.

SUMMARY

The pathogenesis of aortic aneurysms appears to be multifactorial with genetic, histologic, microbiologic, traumatic, and hemodynamic factors each playing a role. Recent studies of matrix proteinases and localization of these enzymes in inflammatory cells may represent a common pathway where a number of etiologic factors exert their influence in the pathogenesis of aneurysms.[22] Genetic mutations causing instability of arterial matrix, hemodynamic forces and atherosclerosis causing arterial enlargement via molecular mediators, and inflammatory cells activating matrix proteases—all describe a dynamic model of the artery wall. Recent developments in molecular biology, histopathology, imaging, endoluminal treatment, and population-based studies are likely further to identify etiologic factors contributing to aneurysmal disease. STI

REFERENCES

1. Clifton M. Familial abdominal aortic aneurysms. Br J Surg 1977;64:756.
2. Tilson MD, Seashore MR. Fifty families with abdominal aortic aneurysms in two or more first order relatives. Am J Surg 1984;147:551.
3. Johansen K, K Koepsell T. Familial tendency for abdominal aortic aneurysms. JAMA 1986;256:1934.
4. Powell JT, Bashir A, Dawson S, et al. Genetic variation on chromosome 16 in association with abdominal aortic aneurysms. Clin Sci 1990;78:128-138.
5. Darling RC III, Brewster DC, Darling RC, et al. Are familial aortic aneurysms different? J Vasc Surg 1989;10:39.
6. Tromp G, Wu Y, Prockop DJ, et al. Sequencing of cDNA from 50 unrelated patients reveals that mutations in the triple-helical domain of type III procollagen is an infrequent cause of aortic aneurysm. J Clin Invest 1993;91:2539.
7. Danks DM, Campbell PE, Walker-Smith G, et al. Menkes' kinky-hair syndrome. Lancet 1972;1:1100.
8. O'Hara PJ, Ratcliff NB, Grove RA, et al. Medial agenesis associated with multiple extracranial, peripheral and visceral arterial aneurysms. J Vasc Surg 1985;2:298.
9. Kontussari S, Tromp G, Kulvaniemi H, et al. A mutation in the gene for type III procollagen (COL3A1) in a family with aortic aneurysms. J Clin Invet 1990;86:1465.
10. Irizarry E, Newman KM, Gandhi RH, et al. Demonstration of interstitial collagenase in abdominal aortic aneurysm disease. J Surg Res 1993;54(6):571-4.
11. Newman KM, Malon AM, Shin RD, et al. Matrix metalloproteinases in abdominal aortic aneurysm: characterization, purification, and their possible sources. Con Tiss Res 1994;30(4):265-76.
12. Newman KM, Ogata Y, Malon AM, et al. Identification of matrix metalloproteinases 3 (stromelysin-1) and 9 (gelatinase B) in abdominal aortic aneurysm. Arterios Thromb 1994;14(8):1315-20.
13. Newman KM, Jean-Claude J, Li H, et al. Cellular localization of matrix metalloproteinases in the abdominal aortic aneurysm wall. J Vasc Surg 1994;20(5):814-20.
14. McMillan WD, Patterson BK, Keen RR, et al. In situ localization and quantification of seventy-two-kilodalton type IV collagenase in aneurysmal, occlusive, and normal aorta. J Vasc Surg 1995;22(3):295-305.
15. Freestone T, Turner RJ, Coady A, et al. Inflammation and matrix metalloproteinases in enlarging abdominal aortic aneurysm. Arteros Thromb 1995;15(8):1145-51.
16. Dustig GJ. Nitric oxide in cardiovascular disorders. J Vasc Res 1995;32(3):143.
17. Glagov S. Hemodynamic risk factors: mechanical stress, mural architecture, medial nutrition, and the vulnerability of arteries to atherosclerosis. In: Wissler RW, Geer JC. Pathogenesis of atherosclerosis. Baltimore: Williams & Wilkins; 1972. p 164.
18. Zarins CK, Glagov S. Atherosclerotic process and aneurysm formation. In: Yao JST, Pearce WH. Aneurysms: new finding and treatments. Norwalk, Connecticut: Appleton and Lange; 1994. p 35.
19. Chuter TAM. Frontiers in vascular disease. Stanford University School of Medicine Seminar; September 1995; Pebble Beach, CA.
20. Brown SL, Busuttil RW, Baker JD, et al. Bateriologic and surgical determinants of survival in patients with mycotic aneurysms. J Vasc Surg 1984;1:541.
21. Tilson MD, Gandhi RH. Arterial aneurysms: etiologic considerations. In: Rutherford RB. Vascular Surgery. Philadelphia; W. B. Saunders; 1995. p 25.
22. Ernst CB, Campbell C, Daugherty ME, et al. Incidence and significance of intra-operative bacterial cultures during abdominal aortic aneurysmectomy. Ann Surg 1977;185:626.
23. Zarins CK. Pathogenesis of aortic aneurysms. In: Ernst CB, Stanley JC. Current therapy in vascular surgery. St. Louis: Mosby; 1995. p 200.