Aortic Aneurysms and Atherosclerosis

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This issue of Circulation has an interesting contribution from Reed et al., who advance the point of view that aortic aneurysms (AAs) are “caused” by atherosclerosis. Although some might believe that this conventional wisdom needs no defense, a dissenting perspective has grown from small beginnings in the late 1970s. Martin was among the first to question whether “dilating” disease of the aorta had different pathogenetic determinants from “stenosing” disease. Busuttil et al. described an increase in proteolytic activity in aneurysmal aorta versus atherosclerotic controls in 1980, and that same year Tilson and Stansel reported differences in the characteristics of patients with AAs versus occlusive disease. Since then, a substantial literature has grown in support of the concept that AA disease has different biochemistry and genetics from occlusive disease. Accordingly, interpretation of the data in the present communication based on the Honolulu Heart Program deserves careful consideration.

The authors propose two arguments in support of a “causal” relation between atherosclerotic risk factors and the development of AAs. First, they show that the traditional risk factors of hypertension, smoking, and cholesterol are associated with an increased incidence of AA. Second, they show that aneurysms have a high score for atherosclerosis in terms of the percentage of aortic surface affected by raised lesions at autopsy. There are alternative explanations for these observations.

First, the authors acknowledge that hypertension and smoking may have stimulated AA formation through pathways other than the promotion of atherosclerosis. In the case of hypertension, it is intuitive that mechanical effects could operate in addition to the mechanism of endothelial injury. For smoking, it is possible that the effect of blocking the active site of \( \alpha_1 \)-antitrypsin might promote the destruction of aortic matrix by endogenous proteases. Like Venn diagrams, the field of smoking may include subsets of AAs and occlusive atherosclerotics, which in turn may overlap each other depending on constitutional susceptibilities to both diseases. It is harder to rationalize the apparent association of serum cholesterol with both diseases. Perhaps the diets of some hypercholesterolemics include tropical oils that may induce a panarterial inflammatory infiltrate. The potential importance of inflammatory cells, especially in the adventitia of AAs, is presently receiving attention. In any case, it is worth noting that approximately 60% of the AAs in the study had serum cholesterol equal to or less than 240 mg/dl, and approximately 40% had serum cholesterol equal to or less than 215 mg/dl. These observations are based on the baseline entry characteristics of the subjects at the time of enrollment in the study and provide a rationale for questioning another recently proposed concept that regression of atherosclerosis is essential for aneurysm formation.

Second, the finding that AAs are atherosclerotic on autopsy examination is not unexpected—so are syphilitic aneurysms and long-standing poststenotic dilatations. The geometry of an aneurysm predisposes to disturbances of flow with boundary layer separation, turbulence, and reversed flow, and, of course, these factors are associated with atherosclerotic degeneration.

The authors make an additional point worth noting. They observe that aortic dissections are probably “age related,” because the peak incidence drops once the “pool of susceptible individuals has been exhausted.” By implication, they suggest that AAs are not age related with a pool of specifically susceptible individuals, because the incidence does not reach a peak in their sample. However, in a study of the prevalence of AAs in a large autopsy series from Sweden, the prevalence appears to peak and then decline after age 80. Although prevalence data based on autopsies may always be criticized for potential selection bias, the same criticism could be raised about the use of autopsy data in the present study.

Beginning with anecdotal reports of familial clustering of AAs in 1977 and 1980, a series of approximately 15 reports beginning in 1984 and continuing to the present leaves little doubt that there must be an important genetic susceptibility factor in the disease. About 20% of AA patients will be aware of another first-order relative with the disease; if male siblings over age 55 are screened by ultrasound, approximately 20–30% will be posi-

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It is presently under study whether the genetic pattern is autosomal dominant, X-linked, or diallelic recessive. A recent report by Majumder et al. cites numerous previous communications and reports that the most parsimonious genetic model is a recessive gene at an autosomal diallelic major locus.

As noted by the authors, the first point mutation in a collagen gene associated with AAs in a non-Marfan family has now been reported. This mutation changed the codon for glycine 619 in the α1-type III procollagen gene to an arginine. As additional mutations associated with AAs are described in the future, it will be interesting to see whether the most common subsets will be in the primary structure of matrix components interfering with their stability or in the expression of proteases and their inhibitors interfering with the balance of matrix synthesis and destruction.

The present article will be applauded by those who wish to see the notion rehabilitated that atherosclerosis “causes” AA and orthodoxy restored. However, this concept has blurred perception of the uniqueness of AA disease as a pathogenetic entity and no doubt delayed for decades original thinking about its etiology. Although the present state of the field may resemble the apocryphal situation of the blind men examining an elephant, we are now on the threshold of insights that may stimulate new approaches for noninvasive diagnosis and for pharmacological innovations to prevent the expression of AA disease in genetically susceptible individuals.

**References**


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