Determinants of Aneurysmal Aortic Disease
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Abdominal aortic aneurysm (AAA) imposes a burden of epidemic proportions. Screening programs in the United States and in Europe have shown that 5% of men >65 years of age have an occult AAA,1 and therefore, an understanding of the determinants of AAA is essential to the design of effective interventions. The article by Forsdahl and colleagues2 in this issue of Circulation specifically addresses this important issue in a cohort of 4345 men and women in Tromsø, Norway. The authors report that male sex, increasing age, and smoking are prominent risk factors for incident AAA in the next 7 years. This is consistent with previously reported studies, which provides reassurance regarding the robustness of the data.3-7 Epidemiological screening studies also suggest a strong association of AAA with atherosclerosis, coronary artery disease, and peripheral arterial disease. The aortic diameter in individuals with AAA detected by screening is rarely of a size associated with a short-term risk for aneurysm-related death (ie, rupture) but rather with a 1.5- to 3-fold increase in cardiovascular morbidity and mortality due to arterial occlusive disease.8,9

An association between aneurysmal and atherosclerotic occlusive disease, both of which are characterized by a chronic inflammatory reaction, matrix degeneration, and vascular tissue remodeling, appears to be obvious, with common risk factors linking them. On closer examination, however, this does not apply to all of them; there are even undeniable exceptions. Smoking is associated with AAA in men 2.5 times more frequently than it is associated with coronary artery disease.10 The role of dyslipidemia remains poorly defined, with some studies claiming a relationship with AAA and others reporting a lack of association.11 Even more strikingly, in contrast to the strong association of diabetes mellitus with arterial obstructive disease, large epidemiology screening studies demonstrated either a negative association or no association between diabetes and AAA.12 In a screening study of 73 451 men, Lederle and colleagues1 found that the detection of an AAA on ultrasound screening was approximately half as likely in patients with diabetes as in nondiabetic patients. Moreover, the progression of AAA was shown to be slower in patients with diabetes, which suggests a pathobiological mechanism by which the aortic media may be protected from aneurysmal degradation in these individuals.12a Interestingly, there is a strong association of AAA with concomitant lower-extremity arterial occlusive disease.7 Although the aorto-iliac axis is particularly susceptible to injury by smoking, the distal arterial tree of the lower limbs appears to be most susceptible to diabetes-related effects. Thus, it appears that smoking and diabetes, which are major risk factors for peripheral arterial occlusive disease, exhibit considerable differences regarding anatomic manifestations.13 It remains unclear whether diabetic and nondiabetic individuals differ in the constitution of the abdominal aortic wall or whether other factors are more relevant. Moreover, the pathobiology of aneurysmal and atherosclerotic occlusive disease exhibits substantial histological differences: Aneurysms include chronic adventitial and medial inflammatory cell infiltration, elastin fragmentation and degeneration, and medial attenuation.14,15 Moreover, aneurysmal disease shows a continuous circumferential destruction of the media, with inflammation first occurring in the adventitial and medial space, whereas classic atherosclerosis is characterized by a scattered distribution of plaques in the subendothelial space.16 Hereditary elements, elastin, and collagen degradation may correlate with genetically unstable proteins or locally increased protease production in aneurysmal lesions. Of note, approximately 25% of cases occur in patients with first-degree relatives who have AAA. This observation supports previous studies implying that a genetic component contributes to the development of AAA.17 Forsdahl and colleagues2 do not report whether there was any familial clustering.

One crucial comment that is therapeutically important concerns the finding by Forsdahl et al1 that the incidence of AAA within 7 years was higher in individuals taking statins at baseline. This is contradictory to experimental data showing downregulation of major mediators of AAA progression by statins.18 In 1994, when the Tromsø study began, statin use was low, with only 1.5% of the population taking statins despite documented cardiovascular disease in 11% of the population. Perhaps only individuals with very high cholesterol levels were treated, and treatment most likely was suboptimal. Unfortunately, lipid levels over time were not reported for patients who were undergoing statin treatment; therefore, it might not be that statin use itself increased the incidence of AAA but that lipid levels in the treated group were still elevated.

Many considerations underscore the complexity of the evaluation of risk factors for AAA. Because the underlying mechanisms remain hypothetical, and no causal relationship can be derived from association studies, answers can only come from therapeutic trials. If interventional studies with risk factor modification indicate a benefit not only for
atherosclerosis-related events but also for AAA incidence, it would be a strong argument for a common causal relationship and would be of great clinical relevance.

Disclosures

None.

References


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