Smoking and Aortic Diseases

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Cigarette smoking is a major vascular risk factor and in this context, it is an independent risk factor for the development of aortic disease, especially the formation and growth of abdominal aortic aneurysms (AAA). Medline was searched up to January 31, 2007 for the relevant literature for this review of the mechanisms by which smoking causes aortic wall damage and its subsequent impact on the clinical manifestation of this process. Idiopathic AAAs and aortic dissection are considered, as well as other aortic diseases (eg, Takayasus, Kawasaki, Behcet and Buerger). There is evidence suggesting an abnormal homeostasis between proteolytic and antiproteolytic activity in the vascular wall during the development of AAAs, and these mechanisms can be influenced by smoking. Smoking cessation plays an important role in the management of aortic disease. (Circ J 2007; 71: 1173–1180)

Key Words: Aneurysm; Aorta; Dissection; Proteases; Smoking

MEDLINE was searched using the words aortic, smoking, aneurysms, inflammation and their combination (access date: 31 January 2007).

Smoking and Atherosclerotic Vascular Disease

Cigarette smoking is a major cause of cardiovascular disease (CVD) and is responsible for approximately 11% of the annual total CVD deaths in the United States. Smoking acts synergistically with other vascular risk factors (eg, hypertension, dyslipidaemia and diabetes) to increase vascular morbidity and mortality. However, smoking has a variable magnitude of increased risk for different vascular diseases: the risk is highest for peripheral arterial disease and aortic aneurysm, and is lowest for coronary artery and cerebrovascular diseases. These effects are thought to reverse after smoking cessation. The constituents of cigarette smoke with the major contribution to pathogenesis of vascular disease are nicotine, carbon monoxide, oxidant gases and polycyclic aromatic hydrocarbons.

Non-smokers who are exposed to "secondhand" smoke experience on average a 30% excess risk of ischemic heart disease and nonfatal myocardial infarction. Secondhand smoke exposure has been shown to activate platelets and to produce endothelial dysfunction, in both experimental animals and humans.

The mechanisms by which smoking causes acute cardiovascular events include endothelial dysfunction, thrombosis and inflammation.

Endothelial dysfunction is an initiating event in atherogenesis, as well as a major factor in causing acute cardiovascular events. Cigarette smoking impairs flow-mediated endothelium-dependent peripheral arterial vasodilatation, an effect that is, at least partly, reversible after smoking cessation. Smokers without atherosclerosis have coronary vasoconstrictor responses to acetylcholine that, in the presence of normal endothelium, produce vasodilatation. Indeed, the oxidant chemicals of smoke degrade nitric oxide (NO) and reduce NO release, with subsequent impairment of vascular dilation and platelet function. Smokers have lower than normal levels of antioxidant vitamins, reflecting their consumption in response to ongoing oxidant stress. In addition, nicotine itself alters the structural and functional characteristics of vascular smooth muscle cells (VSMC) and endothelial cells. Experimental data show that human aortic endothelial cells undergo apoptotic changes when they are exposed to cigarette smoke extracts. This process may be prevented by pre-activation of NO synthase by L-arginine. Furthermore, smoking causes an increase in vascular superoxide production, which results in decreased NO bioactivity and concomitantly increases production of vasoconstrictor eicosanoids. Cigarette smoke extracts, but not nicotine, also inhibit prostacyclin (PGI2: a vasodilator and inhibitor of platelet aggregation) synthesis in human, rabbit and rat vascular tissue.

Smoking-mediated endothelial dysfunction also results in reduced secretion of tissue plasminogen activator (tPA) and increased secretion of plasminogen activator inhibitor (PAI)-1, which results in impaired fibrinolysis. This acts in concert with the increased levels of tissue factor and fibrinogen (both produced by chronic exposure to smoking) resulting in a hypercoagulable state.

Cigarette smoking promotes inflammation, as evidenced by increased levels of circulating leukocytes, C-reactive protein (CRP), interleukin (IL) -6 and acute phase reactants such as fibrinogen. Even secondhand (passive) smoking may contribute to aortic inflammation. Cigarette smoking results acutely in a deterioration of the elastic properties of the ascending aorta in healthy male subjects. Longer term smokers have decreased distensibility of the ascending aorta compared with nonsmokers. The effect of smoking on aortic stiffness and other properties may start very early. Thus, fetal and neonatal nicotine exposure alters vascular functions in adult offspring in a gender-specific manner, which may lead to an increased risk of cardiovascular dysfunction in later life. Furthermore, maternal smoking seems to promote stiffening of the fetal aorta.
during gestation.\textsuperscript{18} Oxidant stress appears to play a major role in the inflammatory response to smoking. For example, oxidized low-density lipoproteins (LDL) and lipid peroxidation products [acting on the platelet-activating factor receptor] stimulate leukocyte adhesion to the endothelium and leukocyte–platelet aggregation.\textsuperscript{19} Nicotine may also contribute to inflammation by acting as a chemotactic agent for neutrophil migration.\textsuperscript{20} Smoking-induced platelet activation may involve increased oxidative stress and is improved within 2 weeks of quitting.\textsuperscript{21,22}

Cigarette smoking is associated with a more atherogenic lipid profile, including decreased levels of high-density lipoprotein-cholesterol and higher levels of LDL-cholesterol levels.\textsuperscript{23} Nicotine, by releasing catecholamines, induces lipolysis and releases plasma free fatty acids with a subsequent rise in triglycerides and very-LDL levels.\textsuperscript{24} The activation of the sympathetic nervous system by nicotine may also contribute to the insulin resistance observed in smokers.\textsuperscript{24}

In addition to alterations in hemostatic factors, endothelial function and blood lipids, smoking influences the hemodynamic properties of the arterial wall. Chronic smokers have higher aortic systolic blood pressure and greater arterial stiffness, in part because of reduced pulse pressure amplification and increased arterial wave reflection.\textsuperscript{25} Passive smoking exerts similar effects.\textsuperscript{26} In addition, when smoking and caffeine intake are combined, they exert a synergistic, unfavorable effect on aortic stiffness and wave reflections.\textsuperscript{27}

Smoking and Abdominal Aortic Aneurysms (AAA)

Clinical Evidence

The prevalence of AAA increases with age\textsuperscript{28} and affects approximately 5% of those older than 50 years.\textsuperscript{29} Several population-based studies established smoking as an independent risk factor for AAA. An analysis of 10 studies including >3 million subjects, the association of “ever smoking” with aortic aneurysmal disease was 2.5-fold greater than that with coronary disease (95% confidence interval (CI), 2.2–2.8) and 3.5-fold greater than that with coronary disease (95% confidence interval (CI), 2.4–5.3).\textsuperscript{30} Furthermore, in a population study of 126,196 subjects, the excess prevalence associated with smoking accounted for 75% of all AAA >4 cm.\textsuperscript{31} In the Edinburgh Artery Study, only smoking was significantly associated with AAA in 34 individuals with screening-detected AAA in whom risk factors were assessed 5 years before screening.\textsuperscript{32} Similarly, in the Malmo Preventive Study, smoking strongly (p<0.0001) predicted the development of large (>5 cm) AAA in middle-aged men.\textsuperscript{33} Moreover, there is evidence that the relationship between smoking and AAA is stronger among older patients (>60 years) with coronary artery disease.\textsuperscript{34}

Another study in men over the age of 50 years showed that current smokers were 7.6-fold more susceptible to AAA than nonsmokers (95% CI 3.3–17.8).\textsuperscript{35} Moreover, ex-smokers were 3-fold more likely to have an AAA (95% CI 1.4–6.4). In the same study, there was a linear dose–response relationship with the duration of smoking; each year of smoking increased the relative risk of AAA by 4% (95% CI 2–5).\textsuperscript{35} Another case–control study showed that, compared with never smokers, the adjusted odds ratio (OR) for AAA (diagnosed by ultrasound) was 2.75 (95% CI 0.8–8.9) for 1–19 pack-years, 7.3 (95% CI 2.4–22) for 20–49 pack-years and 9.5 (95% CI 2.8–32.5) for 50 or more pack-years.\textsuperscript{36}

The impact of each aspect of the smoking habit on the risk of developing an AAA is still controversial. Some studies suggest that the number of cigarettes currently smoked and the depth of inhalation influence aneurysm formation,\textsuperscript{37} whereas others have shown that the duration of exposure rather than the level of exposure determines that risk.\textsuperscript{38}

Studies in humans and mice showed that besides AAA formation, smoking correlates with increased aneurysmal expansion\textsuperscript{38,39} and that quitting smoking could reduce the growth rate of small AAAs.\textsuperscript{40} In addition, the UK Small Aneurysm Trial showed that smokers with impaired lung function had an increased risk of aneurysm rupture and poorer long-term survival.\textsuperscript{41} However, other studies failed to show that smoking influences the outcome of endovascular AAA surgery.\textsuperscript{22,42} A possible explanation for this controversy is that self-reported smoking status may underestimate the effects of continuing smoking on the prognosis of small AAA.\textsuperscript{41} Finally, the occurrence of cognitive dysfunction often observed after elective AAA surgery was significantly (p=0.001) associated with the number of pack-years smoked pre-operatively.\textsuperscript{43}

Pathophysiology

Although AAA is almost always associated with aortic atherosclerosis, the etiologic relationship between atherosclerosis and aneurysms remains controversial. In the Aneurysm Detection and Management (ADAM) study, high cholesterol levels were independently associated with AAA in a multivariate analysis including atherosclerosis.\textsuperscript{34} In addition, a meta-analysis of population-based screening studies showed moderate associations of AAA with a history of myocardial infarction (OR 2.28) and peripheral arterial disease (OR 2.50).\textsuperscript{45} However, there is evidence that patients with AAA have fewer atherosclerotic risk factors (eg, diabetes, hypertension, dyslipidaemia)\textsuperscript{34,36} and different inflammatory activity\textsuperscript{46} than do patients with atherosclerotic vascular disease. Thus, atherosclerosis alone may not be an adequate explanation of the cause of AAA. In fact, studies show that degradation of the extracellular matrix through the action of specialized proteolytic enzymes is an important mechanism in the formation and expansion of AAAs.\textsuperscript{47,48}

Smoking is an initiating factor in the development of aneurysms by affecting elastin degradation. Indeed, AAA development may be aggravated by nicotine-induced neutrophil elastase activity release.\textsuperscript{35} We consider next the interaction of smoking with arterial connective tissue components and the impact in the formation and growth of AAA.

Matrix Metalloproteinases (MMPs)

MMPs are a family of endopeptidases that degrade extracellular matrix components in both physiological and pathological states.\textsuperscript{49} They play an important role in smoking-induced chronic obstructive pulmonary disease (COPD), the second leading cause of smoking-attributable mortality.\textsuperscript{50} There is evidence that MMPs may also contribute to the pathogenesis of smoking-related vascular disease.\textsuperscript{51}

Vascular remodeling depends on degradation and reorganization of the extracellular matrix barriers. Thus, MMPs, which are the main participants in these procedures, allow VSMC migration, a key factor in arterial remodeling after injury.\textsuperscript{52}
Excessive extracellular matrix breakdown is a major determinant of aortic expansion and aneurysm formation. Cigarette smoke induces MMP expression by a large variety of cells (activated macrophages, mast cells, T lymphocytes, endothelial cells and VSMCs) mainly via activation of inflammatory transcription factors. Plasmin activates MMPs and smoking is associated with increased plasminogen activator levels. Experiments in pulmonary tissue showed that MMP-12 mediates smoke-induced inflammation by releasing tumour necrosis factor- from macrophages, with subsequent endothelial activation, neutrophil influx and matrix degradation by neutrophil-derived proteases. On the other hand, reactive oxygen species induce the tissue inhibitor of MMP expression (TIMP). In addition, smoking is associated with increased transforming growth factor- levels by which smoking may inhibit MMP gene expression and induce TIMP expression. Thus, the effect of cigarette smoking on MMP activity is determined by the balance of its effects on MMP and TIMP activities.

Exposure of endothelial cells to cigarette smoke induces expression of MMP-1, MMP-8 and MMP-9. Moreover, increased levels of MMPs-1, -2, -3 and -9 have been reported in patients with AAA. A study showed that MMP-9 mRNA expression is significantly higher in moderate diameter (5–6.9 cm) AAA than in either small (<4 cm) or large (>7 cm) AAA (p=0.03 and p<0.01, respectively). Those authors suggested that increased MMP-9 expression may influence the expansion of AAA >5 cm, but not that of smaller aneurysms. The expansion and high rupture rates of AAA >7 cm may be influenced by the action of other enzymes or by diameter-dependent mechanical stress.

Of note, MMP-9 activity has also been related to aortic stiffness in patients with isolated systolic hypertension, as well as in young, apparently healthy individuals. It is important to note that both MMP activity and MMP-1, -2 and -9 content are decreased in the vascular tissue of diabetic patients. Moreover, diabetes is associated with modification and glycation of collagen and with resistance to MMP digestion. These findings may in part explain the inverse association between the incidence of diabetes and AAA observed in studies. In this context, an interesting association that will need further study is the adverse effect of smoking on the risk of developing diabetes.

Elastase Patients with COPD are more likely to have an AAA and these aneurysms are more susceptible to rupture. In this context, the role of MMPs has already been mentioned. Moreover, the degradation of elastic tissue by elastase in the lungs and the aorta may also be related in the development of AAA in patients with COPD. Specifically, smoking inhibits --antitrypsin, the major inhibitor of elastase and stimulates elastase secretion from neutrophils. Indeed, a study in 79 men with small (3–5 cm), screen-detected AAA showed that all but 1 patient had a significantly (p<0.05) reduced forced first-second expiratory volume (FEV) Smoking was positively correlated with P-Elastase (P-elastase--antitrypsin complexes), --antitrypsin and aneurysmal expansion rate, but not with FEV. The negative correlation between (P-Elastase) and FEV (observed in this study) suggested that impaired lung function was, at least partly, caused by elastolysis. There was no correlation between FEV and expansion rate. This finding may indicate that elastase plays a minor role in AAA, whereas other proteases (MMPs, plasmin, cysteine proteases) have a more significant contribution. The link between COPD and AA is probably more complex than just sharing smoking as a common risk factor. Thus, in 1 study, patients with an AAA (n=89) had more COPD and worse expiratory lung function and forced vital capacity than controls (n=98) However, the association between reduced respiratory function and AAA was not accounted for by cigarette smoking. The authors proposed that activation of inflammation and hemostasis in response to injury may explain the association between AAA formation and reduced respiratory function.

The role of other components of vascular connective tissue has also been investigated. A study in human aortic endothelial cells showed that cigarette smoke extracts reduced 1 of the key enzymes (prolyl-4-hydroxylase) in arterial wall collagen metabolism, which may be responsible for the impaired arterial extensibility and increased likelihood of aneurysm in smokers. Similarly, another study in men (65–72 years) with asymptomatic AAA showed that increased AAA wall distensibility (an important predictor of growth and rupture) was associated with increased elastolysis and decreased collagen turn-over. In this context it is of interest that the aortic augmentation index, a measure of arterial wall reflection and stiffness, is inversely associated with cardiorespiratory fitness in men without coronary heart disease.

Plasmin Plasmin is a common activator of the proteolytic systems involved in aneurysmal degradation and it has been associated with the expansion of AAA. In this context, a study investigated the activating pathways of plasminogen as a predictor of the progression of AAA. Men (n=70) with a small AAA (<3 cm) were scanned annually for a mean of 3.5 years; the annual aneurysmal expansion rate correlated positively with serum levels of PA (p=0.002) and cotinine (a metabolite of nicotine, p=0.038), but not with those of PAI-1 and urokinase-plasminogen activator (u-PA). As serum cotinine levels also correlated positively (p=0.049) with tPA levels, the authors assumed that smoking may promote aortic matrix degradation by activation of plasminogen by tPA, not by u-PA, which usually dominates matrix degradation.

Cysteine Proteases The elastinolytic cysteine proteases, including cathepsins S, K and L, are overexpressed at sites of arterial elastin damage, such as atherosclerotic and aneurysmal lesions. Normal arteries contain little or no cathepsin K or S. In contrast, macrophages in atheroma and smooth muscle cells stimulated by the atheroma-associated cytokines (IL-- and IFN--) secrete active cathepsins S and K.

Protease inhibitors also play a role in arterial wall remodeling by regulating protease activity. Owing to its high concentration in biological fluids, cystatin C is an important extracellular inhibitor of cysteine proteases. An imbalance in cystatin C has been implicated in the aortic wall degeneration observed in AAs. In vitro, alveolar macrophages from cigarette smokers or monocytes stimulated by IFN-- secrete less cystatin C than unstimulated macrophages or monocytes. In vivo, there is an inverse correlation between blood cystatin C levels and aortic dilatation.

The inflammatory response to cigarette smoke may promote cathepsin secretion and inhibit cystatin C expression, resulting in abundant matrix degradation and aneurysmal expansion.

Lipoxygenase Five-Lipoxygenase is the key enzyme in leukotriene biosynthesis and it catalyzes the initial steps in the conversion of arachidonic acid to these biologically active lipid mediators. Studies show that cigarette smoke...
can induce 5-lipoxygenase expression.87–89 The subsequent leukotriene production promotes the adhesion of circulating leukocytes to the vascular endothelium. In mice deficient in apolipoprotein (apo) E, 5-lipoxygenase-positive macrophages constitute the main component of aortic aneurysms.90 On the other hand, 5-lipoxygenase deficiency attenuates the formation of these aneurysms and is associated with reduced MMP-2 activity.83

**Smoking and Inflammatory AAAs**

Inflammatory AAAs are diagnosed by the characteristic clinical triad of abdominal or back pain, a pulsatile (often tender) abdominal mass and an elevated erythrocyte sedimentation rate, as well as by the thick peri-aortic inflammatory “rind” on CT scan. A case–control study84 compared the clinical characteristics of patients who had undergone surgical repair of inflammatory AAA with those of patients who had undergone surgical repair of noninflammatory AAA. Although a history of cigarette smoking was comparable in the 2 groups, more patients with inflammatory AAA tended to be current smokers (p<0.05).84 This finding suggests that cigarette smoking, besides its role in atherosclerosis and elastolysis, may also alter the inflammatory response. Indeed, a study showed persistence of Chlamydia pneumoniae infection in aortic endothelium after smoking exposure.85 Moreover, there is evidence that smoking is associated with raised levels of CRP.86

In general, elevated levels of various plasma markers of inflammation have been reported in patients with AAA, as compared with healthy controls or patients with CVD.87,88 Moreover, cross-sectional studies showed positive correlations between inflammatory markers and the degree of aortic dilatation.89–92 There is also evidence of a strong predictive role of 5 inflammation-sensitive plasma proteins (fibrinogen, orosomucoid, α1-antitrypsin, haptoglobin and caeruloplasmin) for the future development of AAA.93 In 1 study plasma fibrinogen levels were higher in patients with an AAA.94 Those authors also demonstrated positive correlations between AAA size, intraluminal thrombi, and fibrinogen concentration. Smoking was associated with larger aneurysms and intraluminal thrombi.94

It may also be relevant that smoking and plasma fibrinogen and serotonin (a growth factor released from activated platelets) are markers for postoperative infra-inguinal graft stenosis.95

**Smoking and Renal Function in Patients With AAAs**

Multivariate linear regression analysis in 1 study showed that renal function was related to urinary albumin excretion, CVDs, smoking status and kidney size in AAA patients.96 This finding is of interest because renal function can be impaired in AAA patients and raised plasma creatinine levels are considered an emerging predictor of vascular risk.97,98 Moreover, renal dysfunction is a significant and independent risk factor for death after endovascular aneurysm repair.99–101

It is therefore of interest that there is evidence showing that aggressive treatment with statins can improve renal function in high-risk patients and in those with coronary heart disease or peripheral arterial disease.98,102–105 Similarly, there is evidence of an association between statin use and preserved renal function after suprarenal aortic clamping.106

**Smoking and Aortic Dissection**

Aortic dissection, defined as a tear in the intimal layer of the aortic wall, is a life-threatening condition because the aorta may rupture at the point of dissection.107 The Stanford classification divides dissections into 2 groups on the basis of involvement of either the ascending (type A) or descending (type B) aorta.107 There are several etiologies for aortic dissection, including atherosclerosis and its associated risk factors (ie, hypertension, dyslipidemia and smoking), aging, Marfan’s and Ehlers-Danlos syndromes, cocaine use and aortic aneurysms. Several postmortem examinations support that atherosclerosis may be not an important cause of type A aortic dissection, in which atherosclerotic lesions are usually minimal and the prevalence of dissection high.107–111 Furthermore, dissection rarely begins in the abdominal aorta, which is where atherosclerosis is most common. A case–control study in a Japanese population found that smoking and hypoaalbuminemia in addition to hypertension were significantly associated with both type A and type B aortic dissection (p<0.001).12 The frequency of male gender, total protein level, rate of current smoker and alcohol intake were greater for type B than for type A dissection, suggesting there may be different pathophysiologic backgrounds for the 2 groups. However, in another study in which there was a significant (p=0.0003) difference in the growth rate between thoracic and abdominal dissections (4.1 and 1.2 mm/year, respectively), the presence of blood flow in the false lumen was the only significant risk factor for aortic enlargement.113 Finally, smoking may be an important predisposing factor for the rare presence of ischemia of the lower extremities because of aortic dissection.114

**Other Aortic Diseases**

Takayasu arteritis is a chronic inflammatory disease of unknown etiology affecting large vessels, predominantly the aorta and its main branches.115 The clinical features range from asymptomatic disease found as a result of impalpable pulses or bruits, to catastrophic neurological impairment. As inflammation progresses stenotic lesions predominate and tend to be bilateral. Nearly all patients with aneurysms also have stenoses and most have extensive vascular lesions.115 It is still unknown whether smoking influences the pathogenesis and evolution of this arteritis. There is some evidence that the presence of cerebral microembolus is more frequent in smokers with Takayasu arteritis.116

Kawasaki disease (KD) is an acute multisystem vasculitis primarily affecting infants and young children.117 Cardiac and vascular complications (ie, myocarditis, coronary aneurysms) are the most severe manifestations of KD.118 During the acute and subacute phases of the disease, there is activation of different proteinases, resulting in vessel wall weakening and aneurysm generation.117 However, clinically relevant aortic involvement is rare in KD.117 We could not find any literature linking smoking and KD, which may reflect the young age of patients.

Thromboangiitis obliterans (Buerger’s disease) is closely associated with smoking, but this vasculitis seldom affects the aorta.119,120 Nevertheless, there is evidence that Takayasu arteritis and Buerger’s disease are associated with some HLA antigens, which suggests a common pathological pathway.121

Behcet’s disease rarely affects large arteries, but when this occurs the lesions take the form of aneurysms or occlu-
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Circulation Journal Vol.71, August 2007

Those with an AAA) have a high risk of events involving vascular events. In the light of emerging evidence that statins may decrease the rate of progression of AAA, there is something to offer in terms of preventive medicine for these patients. Interestingly, there is some evidence that smoking diminishes the beneficial effect of statins.

The link between smoking and AAA may also point the way for new pharmacological options (eg, MMP inhibitors). Angiotensin-converting enzyme inhibitors (ACEI) normalize impaired bradykinin-mediated, endothelium-dependent venodilation in smokers. This beneficial effect of ACEIs may be related to their antioxidant activity, which could be especially useful in smokers. Angiotensin II receptor blockers (ARBs) may also play a role in aortic disease. Thus, in 1 study of apoE-deficient mice, candesartan but not amlodipine (a calcium-channel blocker) treatment dramatically attenuated the development of atherosclerosis, despite a similar fall in blood pressure. Also, candesartan, but not amlodipine, inhibited aortic expression of inflammatory genes and production of reactive oxygen species. The ARB valsartan improved vascular compliance, but not flow-mediated dilation, in healthy normotensive elderly individuals and losartan reduced monocyte chemoattractant protein-1 expression in the aortic tissues of 2KIC hypertensive rats.

Combinations of 2 drugs may also prove useful. Thus, the combination of pravastatin and olmesartan (an ARB) decreased both surface lesion area and thickness in aortic tissue, producing a greater reduction in aortic cholesterol content than either drug alone in genetically hyperlipidemic rabbits. Pravastatin reduced macropohage infiltration and lip deposition, and olmesartan reduced macrophage infiltration accompanied by a reduction in monocyte chemoattractant protein-1 expression and N-(carboxymethyl) lysine protein adduct, an oxidative stress marker. Another study showed a similar protective role of statin and ARB. The combination of valsartan (an ARB) and perindopril (an ACEI) therapy on aortic arterial stiffness was also beneficial in patients with essential hypertension, left ventricular hypertrophy and high prevalence of nondipping patterns. A comprehensive discussion of the effect of drugs on aortic structure and function is beyond the scope of the present review.

It is most likely that smoking cessation is beneficial for several forms of aortic disease, not only because of a favorable "local" effect but also because some of these patients (eg, those with an AAA) have a high risk of events involving other vascular beds. For example, it is well established that smoking increases the risk of myocardial infarction, stroke and peripheral arterial disease. Smoking cessation may also be of benefit to those who will need to undergo surgery for their AAA or aortic dissection.

Finally, in the light of potentially beneficial lifestyle and pharmacological intervention (smoking cessation and statins), screening for AAA may become cost-effective.

Conclusions

Smoking is an important initiating factor in the development of AAA. In addition to its established role in the atherosclerotic process, it mainly affects elastin degradation in the vascular wall. Smoking promotes the expression of these proteolytic systems while at the same time it attenuates the activity of their inhibitors. However, it is still unclear whether the strong association of smoking with the majority of aortic diseases might be explained by its interaction with proteolytic systems. Improving our knowledge in this field may provide new opportunities for the treatment of vascular disease among smokers.

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Circulation Journal   Vol.71, August 2007


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