Aneurysmal arterial disease is clinically, histologically, and mechanistically quite distinct from atherosclerosis and other occlusive arterial disease. Although atherosclerotic change may be seen in many aneurysms, the relationship is not necessarily a causal one. Aneurysms are more common in some arteries than others, and their pathogenesis varies by location, with, for example, hypertension dominating in cerebral arteries, genetic factors dominating in the ascending aorta, and smoking dominating in the abdominal aorta. Given the importance of smoking in abdominal aortic aneurysm (AAA), this review focuses on AAA. Although there is less evidence implicating smoking in other manifestations of aneurysmal disease, this does not exclude a role for smoking in the development or progression of other aneurysms.

Clinical and Epidemiological Studies of Smoking and AAA

Smoking Increases Prevalence and Incidence

All epidemiological studies of AAA have identified the importance of smoking as a risk factor. Smoking is a very strong risk factor for the presence of an AAA in both men and women, with odds ratios ranging from 3 to 12. In the large (n=114,567) Aneurysm Detection and Management (ADAM) screening study, a history of ever smoking was associated with an odds ratio of 2.97 (95% CI, 2.65–3.32) for 3- to 3.9-cm AAAs and 5.07 (95% CI, 4.13–6.21) for ≥4-cm AAAs. Smoking was considered to be responsible for 75% of the excess prevalence of AAAs ≥4 cm. In a recent report of screening 22,187 Swedish men aged 65 years, 87% of men with AAA were current or ex-smokers, and smoking was the dominant risk factor for AAA (odds ratio, 3.5; 95% CI, 2.4–5.1).

Results from a screening study of >3 million individuals in the United States showed that there was a clear relationship between prevalent AAA and both duration and amount of smoking (Figure 1). There is evidence of a strong linear dose–response effect with duration of smoking. The relationship with the amount smoked is also linear in current smokers and to a lesser extent in ex-smokers. In ex-smokers, the duration seems to be more important than the level of exposure.

The magnitude of risk with smoking eclipses all other modifiable risk factors for prevalent AAA. Intriguingly, smoking seems to be a substantially greater risk factor for AAA than for occlusive atherosclerotic disease. In a systematic review by Lederle et al, the association between smoking and AAA was 2.5-fold (95% CI, 2.2–2.8) greater than the association between smoking and coronary heart disease. The divergent effect of smoking on these 2 vascular diseases supports the distinct pathogenesis of aneurysmal and occlusive arterial disease. The US Preventive Services Task Force considered smoking a sufficiently dominant risk factor for AAA to recommend screening men aged 65 to 75 years who have ever smoked, rather than all men of that age. Kent et al have demonstrated that the efficiency of screening can be improved using algorithms based on risk factors, such as smoking. However, other studies have not supported selective screening based on risk factors.

Although AAA is less common in women, outcomes seem to be worse in women with AAA compared with men with
AAA. There is some evidence that smoking may be a greater risk factor for AAA in women than in men. In the Rotterdam Study, 56% of women with AAA were current smokers compared with 38% of men. In the ADAM study, the odds ratio for ever smoking was 3.80 (95% CI, 1.57–9.20) in women compared with 3.34 (95% CI, 3.04–3.67) in men. It is unclear how important these differences are.

Smoking is also the dominant factor for incident AAA. In a prospective analysis of the Tromsø study, there was a dose–response effect with both smoking duration and quantity. Even individuals who had stopped smoking 10 to 19 years earlier had nearly a 3-fold risk of an incident AAA compared with nonsmokers. This suggests that smoking has a durable effect with both smoking duration and quantity. Continued smoking in individuals with an AAA is associated with increased rates of expansion and the risk of rupture. Smoking is an important cause of progression of AAA.

Influence of Smoking on Intervention and Prognosis
Smoking is relevant when patients require intervention for AAA. For patients undergoing surgical intervention for AAA, current smoking is likely to increase the risk of perioperative death and late mortality. In the UK Small Aneurysm Trial, continued smoking 1 year after randomization was associated with significantly increased mortality (hazard ratio, 3.23; 95% CI, 1.73–6.03). Although smokers are less likely to develop an endoleak after endovascular repair (presumably as a result of prothrombotic effects), they are at increased risk of stent migration.

The recently documented decline in incidence of AAA interventions and deaths and the lower than expected prevalence in screening studies have been attributed to falling rates of smoking. Smoking cessation is associated with a decline in risk of an AAA of ≈30% for each decade after quitting (Figure 1). Nevertheless, the legacy of increased risk of AAA from smoking lasts many decades.

Mechanistic Studies of Smoking and Aneurysm Formation
The most striking feature of AAA histology is the loss of normal medial arterial structure and, in particular, the near complete absence of a normal lamellar elastin matrix, a feature that it has in common with chronic obstructive pulmonary disease. In the aorta, these matrix changes are attributed to 3 general features that are believed to be interrelated: (1) elaboration of high levels of proteases, (2) chronic inflammatory infiltration, and (3) loss/dysfunction of parenchymal cells central to matrix deposition and repair.

Although considerable research with human tissue and animal models over the past 2 decades has begun to inform our understanding of the initiation and progression of AAA, we are yet to develop and verify an effective biological therapeutic that will interrupt development of an AAA or halt the growth of a small AAA. However, given the importance of smoking as a risk factor, there has until recently been very little work on the effects of smoke exposure in these models. Because of the complex make-up of tobacco smoke (TS) and the variety of intermediaries that may be involved, the effects on the vasculature could be mediated through alterations of the inflammatory response, of resident vascular smooth muscle cell (VSMC) function, or of the vessel matrix itself. Several different experimental approaches have been proposed to determine the mechanisms of AAA formation related to smoking (Table).

Human Studies
There are many challenges to evaluating the mechanistic effects of smoking on AAA formation in humans. When looking at the associations of various circulating markers in patients with AAA, Lindholt et al came to the conclusion that smoking may activate tissue plasminogen activator. Because tissue plasminogen activator is a potent activator of elastolytic matrix metalloproteinase, this could link smoking to aortic elastolysis. In support of this, others have shown endothelial response to serum from smokers to result in increased tissue...
plasminogen activator without increased plasminogen activator inhibitor-1 or tissue factor pathway inhibitor-1.44

Genetic variants associated with AAA have also shown potential interactions with smoking. One genome-wide association study found a variant on 3p12.3, which demonstrated that the genetic risk was significantly greater in those with a history of smoking.23 Other studies, however, have not shown a clear relationship among smoking, genetic variants, and AAA.24 It is also possible that smoking contributes to the pathogenesis of AAA via epigenetic interactions, although conclusive evidence about this is still lacking.25

### Studies of Smoke Components

Because the matrix changes in the aorta bear some resemblance to those in the lung, some studies have begun with a presumption that the mechanisms are likely to be similar. Applying techniques that were successfully used to define similar pathological processes induced by TS in the lung,35–41 these studies have attempted to develop a mechanistic understanding of TS on vascular biology. Typically, these studies have relied primarily on gross extracts or purified specific components of TS applied in vivo or to tissues or cells.

Using a water-soluble cigarette smoke extract (CSE) applied to VSMC in culture, the expression of a key component of prolyl-4-hydroxylase is suppressed and thereby reduces collagen production.26 This could promote AAA development by reducing the ability of the aorta to repair medial structural damage. Others have shown that CSE can induce metalloproteinase production and release in vascular cells and inflammatory cells,27,28 thereby promoting matrix damage.

In other studies, however, there is evidence of effects of CSE that would be contrary to what is known about AAA pathology. In VSMC, CSE seems to promote proliferation and survival.42 This would be consistent with the enhancement of intimal hyperplasia caused by smoking, but the VSMC in AAA are typically sparse and senescent and reproduce poorly in vitro.43 Furthermore, the immunomodulatory effects of TS and CSE in the acute situation vary, but it is well described that chronic exposure effectively induces T-cell anergy,44,45 which seems contradictory to the chronic inflammation prominent in AAA.

The cellular effects of nicotine have been well studied and include effects that may both promote and inhibit AAA development, as has been reviewed elsewhere.25 Two recent studies using the apolipoprotein E–deficient mouse model of AAA have shown that nicotine can significantly increase aneurysm formation either with11 or without angiotensin II infusion.30 A similar AAA augmentation has also been shown with nicotine infusion in the elastase perfusion model.31

Activation of the AMP-activated protein kinase α2 (AMPK-α2) in VSMC may be responsible for the nicotine-enhanced AAA formation,30 consistent with increased AMPK-α2 in both smokers and patients with AAA. In a second study, microRNA-21 (miR-21) was found to be enhanced late in aneurysm development in both apolipoprotein E–deficient and elastase perfusion models and was associated with stabilization of further dilation.31 Although nicotine exposure increased miR-21 in the aneurysms and cell culture, AAA in the model was abrogated with administration of exogenous pre–miR-21. The authors did not resolve the apparent contradiction with respect to the effects of nicotine on AAA formation and miR-21.

The relationship between these 2 distinct mechanisms of AAA development related to nicotine exposure remains to be elucidated, although there are some data to suggest that they may be regulated similarly in response to cellular stress. Both miR-21 and AMPK can both be elevated in the context of a stress on glioma cells.47 Further studies of the downstream effects of miR-21 and AMPK, particularly in the context of whole-animal smoke exposure, will probably be necessary to better clarify the role of these molecules in nicotine-enhanced AAA.

### Models Incorporating In Vivo Smoke Exposure

Although smoke component studies do offer important clues to the effects of TS on AAA development, they are often severely limited by 3 assumptions: First, that the toxin or limited toxin mixture applied to the cells in culture (or selected for in vivo exposure) would elicit the same effect as the in vivo response when an individual inhales cigarette smoke. Second, that the components evaluated will elicit the same response when used in a more complex mixture. Third, that TS or TS component exposure may activate known pathways of disease. None of these assumptions has been rigorously investigated or validated.

Models that examine the in vivo effects of smoking on AAA development have a critical role to play with regard to exploring the biological response of the aorta to inhaled smoke and in validating the mechanistic pathways defined by

### Table. Mechanistic Studies of Smoking Components and AAA

<table>
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<tr>
<th>Smoke Component</th>
<th>Study Design</th>
<th>Potential Mechanism</th>
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<tr>
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<td>Circulating inflammatory markers in humans with AAA</td>
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<tr>
<td>Nicotine</td>
<td>Mouse (ApoE-deficient) model of AAA</td>
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<tr>
<td>Nicotine</td>
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AAA indicates abdominal aortic aneurysm; tPA, tissue plasminogen activator; VSMC, vascular smooth muscle cells; and MMP, matrix metalloproteinase.
smoke component evaluations. Unfortunately, although exposure to smoke in the mouse has been used for years to model pulmonary disease, no aneurysm phenotype emerged. Several investigators have demonstrated smoke-enhanced AAA formation with the elastase perfusion model or the angiotensin II–treated apolipoprotein E knockout model.32,48,49

In the elastase perfusion model, like the human disease where the increased risk of aneurysm formation persists decades after cessation of smoke exposure,14 the effects of relatively short exposure to smoke (6 weeks) result in persistently increased AAA development at least 8 weeks after smoke cessation. Somewhat surprisingly, the effects of smoke on aneurysm development are not inhibited with protease inhibitors or through genetic knock-out of elastolytic enzymes.33 The ultrastructure of the aorta is not altered by smoke exposure alone, but smoke exposure increases the T-cell infiltrate in the aorta in response to elastase injury. Even more remarkable was the finding that adoptive transfer of leukocytes from smoke-exposed animals to smoke-free animals confers the enhanced aneurysm phenotype on the recipient.39 These results suggest that durable alterations in leukocyte function, particularly the effects on T cells, may contribute to the enhancement of aneurysm formation by smoking (Figure 2).

Consolidating Current Experimental Results of Smoking on AAA

The impact of the inhalation of a complex cocktail of potential toxins in cigarette smoke on the vasculature presents a significant challenge to scientific interrogation. It must be recognized that the in vivo inhalation of TS results in episodic exposure of combustion products with a variety of bioactivities (eg, oxygen radicals) and affinities with the circulation (eg, lipophilic versus hydrophilic) in the process of delivery to the tissue of interest—the aorta. Cells and enzymes in circulation may also interact with the absorbed smoke in ways that are not well understood. Prominent components of tobacco smoke, such as nicotine, are relatively easy to study in isolation, with some elegant results in cell culture and animals models that can confirm our bias regarding the role of smoking on arterial disease. These studies of individual smoke components must be interpreted with caution, however. The apparent contradictory results of smoke component experiments seen in some of these studies may well be because of unique responses to the simplified exposure chosen (Figure 2). The novel aneurysm models based on inhaled cigarette smoke exposure provide a critical means of validating the potential mechanisms related to smoke components.

Conclusion

There is little doubt that smoking is an important cause of AAA development and progression. It is, however, not the only cause of AAA, with 10% to 15% of cases seen in individuals who have never smoked. This highlights the fact that our understanding of the pathogenesis of AAA is still incomplete. The resistance of smoke-enhanced AAA models to inhibition of elastolytic proteases is an important new clue. An understanding of the unique mechanisms related to smoking is needed to shed light on new strategies to prevent or retard the growth of AAA. Although there is no direct evidence that smoking cessation prevents AAA or decreases the need for AAA intervention, health economic modeling suggests that it would be a cost-effective strategy and it remains a priority for all patients with AAA.50

Sources of Funding

This work was supported by the National Health and Medical Research Council of Australia grants 458505 and1006266 (to P.E. Norman), the National Heart, Lung, and Blood Institute K08 HL84004 (to J.A. Curci), Flight Attendants Medical Research Institute (to J.A. Curci), the American Heart Association 0756432Z (to J.A. Curci), the American College of Surgeons/Society for Vascular Surgery Foundation (to J.A. Curci), the Department of Veterans Affairs (J.A. Curci), and the Peripheral Vascular Surgery Society (J.A. Curci).

Disclosures

None.

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Arterioscler Thromb Vasc Biol. 2013;33:1473-1477; originally published online May 16, 2013;
doi: 10.1161/ATVBAHA.112.300158
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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