Smoking-Induced Vascular Disease
A New Twist on an Old Theme
Peter McNamara, Garret A. FitzGerald

Polycyclic aromatic hydrocarbons (PAHs) are recognized widely as potential environmental procarcinogens and have attracted their share of attention from both funding agencies and scientists interested in biomedical research. Curiously, their potential relevance to cardiovascular disease, rather than cancer, has stirred less emotion. This imbalance of attention is reflected also in society’s response to that most intimate form of self-pollution with PAHs (and much else), cigarette smoking. While the States have chosen to allocate varying proportions of their Tobacco Settlements to research, cancer tends to dominate the agenda. Yet, tobacco-related cardiovascular disease yields an even more striking burden on the public health than cancer. It has been estimated that cardiovascular morbidity and mortality are increased 4-fold in smokers and by one third in passive smokers. One might think that such daunting figures would prompt advocacy groups, such as the American Heart Association, to lobby vigorously at the State level for an appropriate allocation of the Tobacco Settlements to cardiovascular research.

Our understanding of the mechanisms by which smoking mediates cardiovascular injury and the factors that determine interindividual susceptibility to smoking-induced tissue injury is remarkably limited. In this issue of Circulation Research, Kerzee and Ramos2 draw our attention to a mechanism of potential relevance to acceleration of atherogenesis by PAHs, including those in cigarette smoke. The aryl hydrocarbon receptor (Ahr) is a member of the family of basic helix loop helix proteins (bHLHs) that contain PAS domains. This family includes proteins related to differentiation, such as MyoD, the response to hypoxia, such as Hif1α, and circadian rhythms, such as CLOCK, BMAL1, and NPAS2 (which is also known as MOP4). The Ahr is ligated by planar aromatic hydrocarbons via the PAS domain, sheds its chaperones, and heterodimerizes with another bHLH-PAS protein, ARNT (the Ahr nuclear translocator) to drive tran

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Oxidative stress is of likely importance in atherogenesis. Oxidative modification of LDL confers upon it many properties thought relevant to disease progression,6 but oxidation of other protein moieties, such as fibrinogen7 may also be of mechanistic relevance. Interestingly, circulating levels of fibrinogen are elevated in smokers, and smoking conditions the impact of polymorphisms in the fibrinogen gene on levels in the circulation.8 DNA and lipid targets of oxidation may also be of relevance; for example, CYP1B1 has been implicated in the formation of DNA mutagens.9 Efforts to implicate oxidative stress as a mechanism of disease in vivo have been hampered by the nonspecificity of the indices, their chemical lability, and limitations of the analytical procedures applied.

Isoeicosanoids are a family of free radical–catalyzed isomers of eicosanoids, the enzymatic products formed from arachidonic acid by cyclooxygenases, lipoxygenases, and CYPs. The chemical stability of isoeicosanoids, their route of formation, and susceptibility to sensitive and specific measurement by mass spectrometry have rendered them attractive as indices of lipid peroxidation in vivo.10 Interestingly, urinary isoeicosanoids are increased dose dependently in active smokers and in those exposed to passive smoke,11,12 as well as in patients with hypercholesterolemia.13 Suppression of elevated isoeicosanoids (but not cholesterol) in hypercholesterolemic mice retards atherogenesis,14 affording a proof of principle of the importance of oxidant stress in plaque progression. Sidestream smoke increases the rate of atherogenesis in mice.15 However, the contribution of oxidative stress to disease progression is unknown. In humans, controlled studies of the impact of smoking on progression of plaque burden using modern imaging methodology, such as electron beam computerized tomography, have yet to be reported. However, a surrogate of overt atherosclerosis, endothelial dysfunction, is reported in smokers and in those exposed to passive smoke, for as little as 30 minutes.16,17 Oxidative stress may contribute to this response. Thus, smokers are depleted in endogenous vitamin C (but not E), and supplements of vitamin C (but not E) both depress their elevated isoeicosanoids11 and restore endothelial function.18

So much for oxidative stress as a link between exposure to cigarette smoke and progression of underlying vascular dis-
ease. While it may be relevant to chronic stable angina and perhaps to ischemic cardiac decompensation, might oxidative stress also contribute to acute vaso-occlusive syndromes in smokers, such as unstable angina, myocardial infarction, and sudden cardiac death? Here we have much less evidence, as the mouse is a notoriously poor model of plaque instability and consequent thrombotic vascular occlusion. However, urinary isoeicosanoids are increased during the ischemic phases of unstable angina and levels are raised in the atherosclerotic plaques of those patients who progress to revascularization procedures. Furthermore, oxidants, such as H$_2$O$_2$, and several isoprostanes, may activate platelets and induce vasoconstriction. Smokers exhibit evidence of hemostatic activation. For example, urinary thromboxane metabolite excretion is dose dependently increased in apparently healthy smokers and falls on quitting, and levels also track with smoking on analysis of monozygotic twins discordant in their smoking habit. Finally, perhaps oxidant stress also conditions the timing of acute vascular events. The ability of the bHLH-PAS protein Npas2 to function as a core component of the clock mechanism in brain cells has recently been shown to be regulated by the NAD:NADPH ratio, implicating oxidant stress as a critical switch in the ability of this protein to function in the clock feedback loop and to regulate circadian gene expression.

Although retrospective analyses suggest that those individuals who consume a diet rich in antioxidants have a reduction in cardiovascular mortality, prospective clinical trials of antioxidants, for the moment, present a confusing picture. For example, while vitamin E seemed effective in reducing acute events in the CHAOS trial, it was apparently ineffective in both GISSI-2 and HOPE. This may suggest that oxidative stress is of marginal relevance to plaque destabilization, that supplements are less effective than vitamin-enriched diets, or that other covariants of such diets explain the epidemiology. However, none of the prospective trials included a biochemical basis for patient or dose selection. As the response to exogenous antioxidants is highly conditioned by the degree and specificity of depletion of endogenous antioxidant defense, as exemplified in smokers, inclusion of inappropriate patients may have undermined sample size calculations and the power of the analyses. Certainly, these trials should not be the last word on the role of oxidant stress in cardiovascular disease.

Kerzee and Ramos draw our attention to a new potential twist on an old mechanism. Their work highlights particularly our limited insight into how free radicals might modulate the expression of both acute and chronic phenotypes of smoking-induced vascular disease. It provokes interest in the possible role of CYP-catalyzed products in disease expression, poly- morphic variation in CYPs as a contributor to individual susceptibility to smoking-induced vascular injury, the downstream target enzymes induced via CYP activation, and the direct and indirect mechanisms by which free radicals modulate expression of genes relevant to plaque stability.

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