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REVIEW ARTICLE

Pathophysiologic Mechanisms of Tobacco Smoke Producing Atherosclerosis

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Abstract: ***Introduction*:** Despite the convincing epidemiologic association between smoking and vascular disease, the pathophysiologic mechanisms by which smoking initiates and contributes to the progression of atherosclerosis remain incompletely understood. A precise dose-dependent correlation has never been demonstrated, suggesting that the biological relationship is complex and influenced by individual genetic and possibly environmental factors. Although endothelial dysfunction and intimal damage appear to be central to atherogenesis, how tobacco products cause this effect has not been established. The purpose of this review is to describe the current state of knowledge of the main pathophysiologic pathways of how tobacco smoking abets atherosclerosis

***Constituents of Tobacco Smoke*:** Tobacco combustion produces a mixture of organic substances derived from burning organic materials. The predominant gaseous phase constituents include carbon monoxide, acetaldehyde, formaldehyde, acrolein, and other carbonyls, as well as nicotine and tobacco-specific nitrosamines.

***Potential Pathophysiologic Mechanisms*:** Smoking-induced changes in coronary vasomotor tone, platelet activation, and endothelial integrity are major components of both the development of atherosclerosis and its clinical presentation. Smoking may initiate and accelerate the progression of atherosclerosis by injuring the vascular intima. Other potential mechanisms include intimal damage and endothelial dysfunction, oxidative stress and injury, thrombosis, lipid abnormalities, and inflammation.

***Conclusion*:** Smoking tobacco products contributes measurably to the incidence of acute vascular events and chronic disease. The causative compound, the exact mechanism of injury, and whether the atherogenic effect is modifiable are not known.

Keywords: Smoking, tobacco, pathogenesis, atherosclerosis, nicotine, vascular disease.

1. INTRODUCTION

Smoking is the most important modifiable risk factor associated with atherogenesis. Tobacco has been implicated in the origin and progression of the atherosclerotic process by numerous population-based studies [1-5]. Tobacco smoking is associated with atherosclerosis, most prominently by contributing as a risk factor for myocardial infarction and coronary artery disease (Table **1**) [6]. Low-tar and nicotine cigarettes, smokeless tobacco, and passive smoking are also associated with an increased risk of vascular disease [7-11].

Despite the convincing epidemiologic association between smoking and vascular disease, the pathophysiologic mechanisms by which smoking initiates and contributes to the progression of atherosclerosis remain incompletely understood. A precise dose-dependent correlation has never been demonstrated [1, 4], suggesting that the biological relationship is complex and influenced by individual genetic and possibly environmental factors. Although endothelial dysfunction and intimal damage appear to be central to atherogenesis, the precise mechanism by which tobacco products cause this effect has not been established. The purpose of this review is to describe the current state of knowledge of the main pathophysiologic pathways of how tobacco smoking abets atherosclerosis.

Table 1. Vascular manifestations of tobacco-related atherosclerosis.

• Stable ischemic heart disease (including exacerbation of angina pectoris)
• Myocardial infarction
• Stroke
• Aortic aneurysm
• Peripheral arterial disease (including intermittent claudication, vascular thrombosis and limb loss)
• Erectile dysfunction
• Vasospastic angina
• Cardiac arrhythmia
• Heart failure
• Sudden cardiac death

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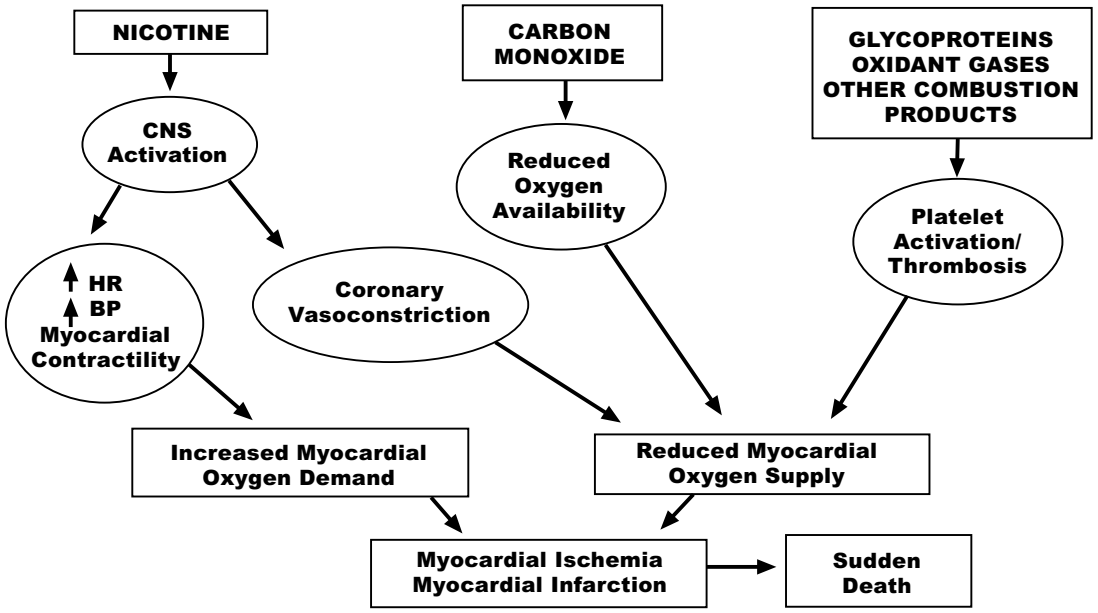

Fig. (1). Figure reproduced from benowitz [1].

2. COMPONENTS OF TOBACCO SMOKE

Over 7000 chemical constituents in tobacco smoke have been identified; of these, about 400 are detected routinely in mainstream and sidestream smoke [12-14]. Tobacco combustion produces a mixture of organic substances derived from burning organic materials. The predominant gaseous phase constituents include carbon monoxide, acetaldehyde, formaldehyde, acrolein, and other carbonyls, as well as nicotine and tobacco-specific nitrosamines [15]. These chemicals are further modified by detoxification systems, such as the cytochrome P450 system. Commercial tobacco products contain additional compounds, and their combustion chemistry is unstudied. However, the precise mechanisms of how particular substances contribute to the initiation, progression, and outcome of atherosclerotic disease have not been delineated. It is likely that the inciting constituents of cigarette smoke are not of one compound or class but rather are due to a mixture interacting with genetic and environmental influences [2, 3].

Cigarette smoke drawn through the tobacco into the mouth is termed mainstream smoke. Sidestream smoke is the smoke that emanates from the burning end of a cigarette. Mainstream cigarette smoke comprises 8% tar and 92% gaseous components. Tobacco smoke is the combination of sidestream smoke (85%) and exhaled mainstream smoke (15%). Sidestream cigarette smoke contains a higher concentration of the toxic gaseous component than mainstream cigarette smoke [5, 9, 16, 17].

The two best studied substances in smoke are nicotine and carbon monoxide (CO). While their physiologic effects have been studied for decades, no mechanism directly links these to the pathophysiology leading to atherosclerosis [5, 15]. Although other gaseous constituents have been linked generally to atherosclerosis, no mechanisms have been hypothesized or elucidated.

Carbon Monoxide (CO). Serum carbon monoxide levels are increased in smokers. When CO is inhaled, it combines with hemoglobin to form carboxyhemoglobin. CO binds to the same sites as oxygen but with 210 times more affinity. Carboxy-hemoglobin releases carbon monoxide slowly so that less hemoglobin is available to transport oxygen, which greatly diminishes hemoglobin's oxygen-carrying capacity. As a result, small amounts of CO can substantially reduce hemoglobin's ability to transport oxygen, resulting in diminished oxygen carrying capacity. This may be a critical concern in patients with severe coronary and peripheral artery disease or congestive heart failure (Fig. **1**). Chronic hypoxia also leads to compensatory polycythemia, which increases blood viscosity and contributes to a prothrombotic state.

Nicotine. The most well-studied substance in cigarette smoke impacting the cardiovascular system is nicotine. Nicotine is a component of the tar phase. The addictive quality of tobacco is largely due to nicotine and related alkaloid content. Some chemical constituents of tobacco, such as ammonia, indirectly influence the toxicity of smoke by increasing the pH of inhaled smoke and, therefore, facilitate the absorption of nicotine. Nicotine inhaled from cigarette smoke is absorbed over a large surface area of the lungs and is transported to the brain in 10–20 seconds via pulmonary venous absorption directly to the left heart. A typical cigarette contains 20 mg of nicotine, of which about 2.5 mg is absorbed, with a half-life of about 2 hours. 80-90% is metabolized hepatically. About 80% of nicotine is broken down to cotinine by enzymes in the liver (*e.g.*, CYP2A6). Nicotine is also metabolized in the lungs to cotinine and nicotine-N-oxide. Cotinine and the remaining nicotine are filtered from the blood by the kidneys and excreted in the urine.

Smokeless tobacco users likely take in as much nicotine per day as smokers, but the kinetics are much slower [11]. Nicotine derived from the gum, lozenges, inhalers, and nasal spray is absorbed through the oral or nasal mucosa, entering the venous circulation. These forms of intake cause nicotine levels to peak in the order of minutes, while transdermal patches release nicotine more gradually to peak concentrations within hours after application

Nicotine is a sympathomimetic that is a direct agonist of nicotinic acetylcholine receptors [α2-adrenergic receptor], located in the plasma membranes of certain neurons and on the postsynaptic side of the neuromuscular junction. These receptors are found in the central and peripheral nervous system, muscle, adrenal gland, and brain. They are the primary receptor at the neuromuscular junction mediating motor nerve-muscle communication that controls muscle contraction [5].

Nicotine is primarily responsible for increases in cardiac output, heart rate, and blood pressure during smoking [15]. The rapid increase in heart rate and elevation in blood pressure occurs as a result of direct stimulation by nicotine of peripheral postganglionic adrenergic receptors and carotid and aortic body chemoreceptors. Nicotine activates the sympathetic nervous system by increasing the release of adrenal catecholamines and by increasing peripheral sympathetic nerve activity. Adrenal hormones are released almost immediately with the onset of smoking and likely participate in the systemic hemodynamic response. Nicotine also has proven vasoconstrictive effects on coronary circulation [18-20]. The possibility of nicotine signaling in the vascular wall, with activation of the nicotinic acetylcholine receptors, increasing permeability, has been suggested [21].

Nicotine alters the shape of endothelial cells and reduces prostacyclin production. Increased endothelial cell proliferation and intimal hyperplasia have been observed in animal experimental studies. Interestingly, tobacco smoke has a much greater effect than nontobacco smoke on circulating endothelial cells and platelets, suggesting the involvement of components of tobacco smoke. However, the mechanism of this effect is complex: people exposed lifelong to smokeless tobacco and high levels of nicotine do not have accelerated atherosclerosis. Nicotine causes acute endothelial dysfunction, although to a significantly smaller extent than cigarette smoke. There is little doubt that nicotine and smoking cause endothelial dysfunction and damage the intimal layer. Free radicals contained in the tar and gas phase of cigarette smoke can damage the vascular endothelium, but a direct link to plaque rupture has not been established [20, 22-25].

Although no direct contribution of nicotine to smoking-related atherosclerosis has been demonstrated, it likely does contribute to the occurrence of acute cardiovascular events via its effects on increasing demand and limiting supply [15]. Current evidence suggests that the effects of nicotine are much less important than are the prothrombotic effects of cigarette smoking or the effects of CO. Nicotine itself does not appear to enhance thrombosis [1, 26]. In various models, although high doses of nicotine are associated with atherogenic changes, the majority of current evidence suggests that nicotine, at concentrations similar to a smoker's blood level, has a minor effect on the initiation or propagation of atherosclerosis [5, 20].

Thiocyanate and Aromatic Amines. The potential roles of these compounds have been discussed for decades, but no definitive evidence exists to implicate them directly in smoking-induced arterial disease [27]. Thiocyanate is a known combustion product of tobacco in small quantities and is metabolized to hydrogen cyanide, which is toxic to endothelial cells. Aromatic amines certainly are carcinogenic and may raise blood pressure, but any link to the pathophysiology of smoking is conjectural.

3. CLINICAL AND PATHOPHYSIOLOGIC EFFECTS OF SMOKING

Hemodynamic Response to Smoking. The systemic hemodynamic response to smoking results from direct effects as well as influences on autonomic and peripheral ganglia, systemic hormonal release, myocardial wall stress, and contractility. Cigarette smoking increases heart rate, systolic blood pressure, myocardial contractility, and cardiac output at 1- 2.5 minutes after the start of smoking, with a peak hemodynamic response after 5 minutes. These effects start within seconds, preceding catecholamine release from the adrenal cortex [15, 20, 28-32].

Myocardial wall stress increases consequent to increased afterload produced by elevated blood pressure. Systemic catecholamine release causes increased contractility and further increases in heart rate beyond nicotine's direct positive chronotropic effect. Thus, cardiac output increases chiefly as a result of increased heart rate, with variable changes in stroke volume. All of these physiologic responses to smoking increase myocardial oxygen demand. Under these circumstances, increased coronary blood flow must occur to maintain the balance between supply and demand, as oxygen extraction by the myocardium is maximal at rest [15, 20].

The neural and hormonal mechanisms that mediate this response are well described [18]. Sympathetic ganglionic stimulation and activation of alpha-adrenergic neural reflexes result in peripheral vasoconstriction. The increased peripheral resistance elevates blood pressure. Direct chronotropic effects and adrenal catecholamine secretion raise the heart rate. Myocardial contractility increases because of the catecholamine effect, but changes in stroke volume vary considerably. Cardiac output increases primarily as a consequence of the increased heart rate.; stroke volume changes are variable.

Smoking induces the release of catecholamines from the adrenal medulla and adrenergic terminal nerve endings. An early increase in serum norepinephrine levels is followed by an increase in serum epinephrine levels [15, 21]. These cardiovascular effects are also due to the stimulation of sympathetic neurotransmission by nicotine, which stimulates catecholamine release by activation of nicotinic acetylcholine receptors localized on peripheral postganglionic sympathetic nerve endings.

Vasomotor Dysfunction in Peripheral and Coronary Arteries. Smoking impairs limb flow-mediated vasodilation [FMD] of the brachial artery in a dose-dependent manner, demonstrating vascular dysfunction. The reduction of endothelium-dependent dilatation by smoking is reversible. Smoking low nicotine cigarettes impairs FMD as much as smoking regular cigarettes, suggesting that nicotine is not the only factor mediating vasoconstriction. FMD impairment is due to a significant reduction of NO bioavailability in the vasculature [21, 33-35].

Smoking is associated with diminished coronary vasodilator reserve [36] and has a demonstrative vasoconstrictive effect, especially notable in the presence of severe proximal

stenosis [28]. Diminished endothelium dependent coronary vasodilation has also been demonstrated [37]. Smoking causes vasoconstriction of proximal and distal epicardial coronary arteries and an increase in coronary resistance and vessel tone. The diminished local flow despite an increase in myocardial oxygen demand may produce transient mild ischemia [15, 32].

Smoking-induced changes in coronary vasomotor tone, platelet activation, and endothelial integrity are major components of both the development of atherosclerosis and its clinical presentation. Smoking may initiate and accelerate the progression of atherosclerosis by injuring the vascular intima. Mechanical damage, possibly as a result of persistently increased coronary artery tone and frequent episodes of hemodynamic stress, has been hypothesized, similar to that postulated for hypertension [38]. Thus, smoking-induced vasoconstriction and enhanced platelet aggregation at the site of a severe coronary lesion may partially explain the increased incidence of acute cardiac events in chronic smokers and the improved prognosis of those who quit.

Plaque rupture. Although it is highly likely that increased vasomotor tone contributes to plaque rupture, no definite mechanistic connection between the physiologic effects of tobacco products and plaque rupture has been proven. Nevertheless, smoking is strongly associated with acute myocardial infarction. A relationship between cigarette smoking and the development of vulnerable coronary artery plaques using virtual histology intravascular ultrasound [VH-IVUS] has been shown [39]. Cigarette smoking is associated with a higher burden of necrosis in the core of plaques (20.7 *vs*. 17.2%, p=0.04) and is independently associated with a 4.54% increase in the quantity of necrotic core (p=0.01). This compositional difference may partially explain the clinical sequelae of smoking since the burden of necrotic atherosclerotic plaque predicts vulnerability and the likelihood of plaque rupture.

The "smoker's paradox" is the unexplained lower mortality and morbidity in smokers *vs.* non-smokers with myocardial infarction. It is most likely an epiphenomenon caused by different baseline characteristics of smokers and nonsmokers [40, 41]. Younger MI patients have more acute plaque rupture but less extensive coronary atherosclerosis and fewer risk factors than older patients. The critical point is that smoking causes myocardial infarction at an earlier age in smokers compared to non-smokers.

Lipids. Smokers have significantly higher serum cholesterol, triglyceride, and low-density lipoprotein [LDL] levels compared to nonsmokers. Smoking alters lipoprotein metabolism, particularly increasing the generation of oxidized LDL [2, 42-47]. High-density lipoprotein and apolipoprotein A1 levels are decreased in smokers. There is also a significant association between secondhand smoke inhalation and abnormal serum lipids [45].

Apart from modulating lipid quantities, smoking also impacts lipids qualitatively. Free radicals and oxidants present in cigarette smoke contribute to lipid oxidation and to an increase in oxidative metabolism. An increased presence of lipid peroxidation products in the serum of smokers has been reported, as have increased levels of circulating autoantibodies against oxidized LDL [2, 48, 49]. Peroxynitrite, which is generated by a reaction between NO and superoxide, has been implicated in the oxidation of LDL in smokers [50, 51]. Smokers demonstrate significant evidence of increased lipid oxidation, signs of oxidative stress, and impairment of antioxidant systems [2], but it has not been demonstrated whether this represents the specific mechanism of endothelial damage.

Interaction with other risk factors. Cigarette smoke aggravates other risk factors for atherosclerosis. Smoking raises systolic and diastolic blood pressure, worsening hypertension and requiring more drugs for control, but there is a paucity of data suggesting that smoking actually causes hypertension. Similarly, smoking is associated with, but not necessarily a cause of hyperlipidemia, hyperglycemia, and insulin resistance [52].

4. EFFECTS ON INITIATION AND PROGRESSION OF VASCULAR DISEASE

Despite the overwhelming epidemiological evidence linking cigarette smoking with cardiovascular disease, the precise components of cigarette smoke responsible for its causation and the mechanism by which they exert their effects have not been elucidated [2, 22]. Mechanisms by which smoking may contribute to acute vascular events are summarized in Table **2**.

Table 2. Mechanisms of tobacco related physiological effects.

- Carbon monoxide–mediated reduced oxygen-carrying capacity of the blood oxygen transfer and dissociation from hemoglobin
- Hemodynamic stress & increased myocardial work
- Stimulates the sympathetic nervous system & catecholamine release
- Increases coronary artery tone/vasoconstriction
- Endothelial cell damage, Damage cells that line the blood vessels & vascular dysfunction
- Vasomotor dysfunction
- Oxidative stress, & injury
- Plaque Rupture
- Vascular inflammation
- Induction of a hypercoagulable state platelet activation & Coagulation: Prothrombotic and more likely to clot, which can block blood flow to the heart and brain
- Increased fibrinogen and blood viscosity, increased stickiness
- Worsens Lipid profile
- Increased insulin resistance & synergism with other CAD risk factors

Intimal damage and endothelial dysfunction. Endothelial dysfunction is produced by reactive oxygen species [ROS] that leads to endothelial cell loss by apoptosis or necrosis [2, 22]. Smoking damages the endothelium leading to measurable vascular dysfunction. Endothelial dysfunction, including an increase in permeability and decreased nitric oxide [NO] production, along with increased expression of adhesion molecules and adherence of leukocytes to the vessel wall, is a common mediator of many CAD risk factors. Endothelial injury is generally the initiating event in the

pathogenesis of atherosclerosis and it has been the "working hypothesis" for decades that components of cigarette smoke damage the endothelium [22, 52]. It must be emphasized, however, that, perhaps surprisingly, no definitive evidence exists to prove the concept, despite consistent in vitro studies.

Cigarette smoke damages the vascular endothelium mechanically. Endothelial cells contract, mediated by oxidation and collapse of the tubulin system. This response may be reversible and may be the cause of the reduction of FMD, but perhaps results in endothelial cell death. In addition, smoking induces tissue remodeling, with the functional consequence of increased permeability of the endothelial cell layer [2]. A simple but attractive proposition is that chronic smoking predisposes to accelerated coronary atherosclerosis, at least in part, as a consequence of a cumulation of its acute effects on coronary vasomotor tone [38]. Frequent episodes of acute vascular stress may lead to recurrent coronary vasoconstriction, creating intimal damage.

It is likely that although, the substances in the smoke are causing the damage. All forms of cell death (apoptosis, necrosis, programmed necrosis, and autophagy) are induced by cigarette smoke combustion products. Endothelial cells release inflammatory and proatherogenic cytokines in response to smoke. Endothelial cell morphology and function were altered by CO exposure. CO exerts growth arrest in smooth muscle cells in the vascular endothelium by inhibiting the cell cycle transition from G0/G1 phase to the S phase and has a regulatory effect on cell apoptosis through the expression of apoptosis-associated genes [2, 22, 52].

Oxidative Stress & Injury. Cigarette smoke contains a large number of oxidants, which raises the possibility that its atherogenic effects are a consequence of oxidative damage to the vascular endothelium. Supportive evidence is that antioxidants such as ascorbic acid reverse flow mediated endothelial dysfunction [53]. For these reasons, it has been hypothesized that free radicals in smoke mediate oxidative stress, contributing to the initiation and progression of atherosclerotic disease [5, 52, 54). The main free radical in the tar phase is the quinone/hydroquinone complex, which is a redox system that reduces molecular oxygen to produce superoxide. The second free radical of note is in the Gas phase: small oxygen and carbon centered radicals produced by the oxidation of nitric oxide (NO) [22]. It has also been shown that aldehydes in smoke increase reactive oxygen species production by activating NADPH oxidase. Moreover, compounds in tobacco smoke increase eNOS acetylation and expression and decrease and uncouple eNOS activity [54-57].

Free radicals such as superoxide and NO decrease NO availability and generateperoxynitrite, which further enhances cellular oxidative stress [16]. Antioxidants and agents that increase NO availability have been shown to either improve or reverse the proatherogenic, proinflammatory, and prothrombotic attributes associated with CS [5, 54, 58-62]. Chemicals in smoke chemicals lead to adhesion molecule expression on the surface of endothelial cells and induce the release of proatherogenic cytokines, such as interleukin-6 and interleukin-8. The core of these processes is the activation of the NFkB cascade [2, 5].

Inflammation. Smoking activates the immune system both systemically and locally in the arterial milieu. Smokers have significantly increased serum levels of cytokines that enhance inflammation, including tumor necrosis factor-α, interleukin-1β, and serum C-reactive protein. Interestingly, pro-inflammatory markers are increased in both active smokers and those exposed to secondhand smoke [2]. Cigarette smoking increases thromboxane and decreases prostacyclin production, causing vasoconstriction and platelet aggregation. Moreover, soluble VCAM-1, ICAM-1, E-selectin levels are higher in smokers. Plaque formation and the development of vulnerable plaques may also result from smoke enhancing the activation of matrix metalloproteases [52]. The recent MESA trial showed an association between high levels of high sensitivity C-reactive protein in smokers to be associated with atherosclerosis [63].

Platelet Activation and Thrombosis. Smoking increases the activation, adherence, and aggregation of platelets, further favoring the development of a procoagulant and inflammatory environment. Smoke also increases the number of platelets, which likely increases the risk of thrombosis [2]. Smoking also has been shown to increase fibrinogen levels and blood viscosity [64]. Not only does this affect flow dynamics, but also the increased stickiness predisposes to thrombosis. Perhaps these mechanisms contribute to the risk of MI and stroke, which are acute thrombotic processes.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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CONCLUSION

Smoking tobacco products contributes measurably to the incidence of acute vascular events and chronic disease. The precise compound, the exact mechanism of injury, and the question of whether the response is modifiable are all unknown.

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