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Pathophysiological Mechanisms of Tobacco-Related CVD

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Cigarette smoking is a leading preventable risk factor for the development and progression of cardiovascular diseases (CVDs). Epidemiologic studies conclusively prove that both active smoking and second-hand smoke contribute significantly to morbidity and mortality related to CVD. Cigarette smoke is a mixture of several toxic chemicals, of which nicotine, carbon monoxide, and oxidant chemicals are most commonly implicated in the pathogenesis of cardiovascular disease. Tobacco causes endothelial dysfunction, inflammation, insulin resistance, alteration of lipid profile, hemodynamic alterations, and a hypercoagulable state. All of these act synergistically as pathobiologic mechanisms of atherothrombosis in tobacco users.

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Smoking is a major cause of death from cardiovascular disease. Several epidemiologic studies unequivocally prove that cigarette smoking increases the incidence of coronary artery disease (CAD) [1–6]. According to World Health Organization (WHO) estimates, nearly 5.4 million premature deaths a year are attributable to tobacco smoking worldwide [7]. If current trends continue, 10 million smokers per year are anticipated to die by 2025 [8,9]. Approximately 35–40% of smoking-related deaths are due to cardiovascular diseases [10,11]. Moreover, exposure to environmental tobacco smoke (secondhand smoke) poses a significant cardiovascular health hazard. Secondhand smoke has been shown to increase the risk of developing CAD by 25–30% [12]. Although the link between CAD and smoking is clear and conclusive, the mechanisms by which it occurs are not completely understood. Several factors may be involved because smoking has a variety of effects that may contribute to thrombosis and atherogenesis. This paper outlines the various postulated pathophysiological mechanisms involved in tobacco-related cardiovascular disease.

COMPONENTS OF CIGARETTE SMOKE

Tobacco smoke is a toxic mixture of more than 5,000 chemical compounds [13,14]. Cigarette smoke is a complex aerosol consisting of vapor and particulate phases [15]. The particulate phase is

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the material that is trapped when the smoke stream is passed through the cigarette filter, whereas the vapor phase material passes through the filter. The major vapor phase constituents include carbon monoxide, acetaldehyde, formaldehyde, acrolein, nitrogen oxides, and carbon dioxide, whereas nicotine and various particulate matters (collectively known as "tar") constitute the major particulate phase components of cigarette smoke. Terms commonly used to describe the smoke coming from a cigarette are mainstream smoke, side stream smoke, and secondhand or environmental tobacco smoke. Cigarette smoke that is drawn through the tobacco into an active smoker's mouth is known as mainstream smoke [16]. Side stream smoke describes the smoke coming off the end of a smoldering cigarette. When combined, side stream smoke and a small fraction of exhaled mainstream smoke form secondhand smoke, also known as environmental tobacco smoke. Side stream smoke contains a relatively higher concentration of the toxic gaseous component than mainstream cigarette smoke does.

ROLE OF VARIOUS COMPONENTS OF TOBACCO SMOKE IN CARDIOVASCULAR DISEASE

The constituents of cigarette smoke that have received the greatest attention, as potential contributors to cardiovascular disease are nicotine, carbon monoxide, and oxidant gases. There has also been some research on polycyclic aromatic hydrocarbons and other constituents of tobacco smoke that may contribute to atherogenesis [17].

Nicotine. Nicotine, one of the most studied constituents of cigarette smoke, is a potent ganglionic and central nervous system stimulant. Each puff contains approximately 50 µg of nicotine. Nicotine exerts its cardiovascular effect via sympathetic neural stimulation [18,19]. The hemodynamic effects of cigarette smoking are mediated primarily by nicotine. Nicotine increases heart rate, blood pressure, and cardiac output, leading to an increase in myocardial oxygen demand. It increases heart rate both acutely (up to 10–15 beats/min) [20], as well as throughout the day with regular dosing (average increase 7 beats/min as measured on ambulatory monitoring) [17]. Whether nicotine plays a direct role in the development of atherosclerosis is still unclear. It has been reported to have variable effects on nitric oxide [21,22], which may contribute to endothelial dysfunction in tobacco users [23].

Carbon monoxide. Carbon monoxide (CO) is inhaled in cigarette smoke. Although previously thought to be responsible for the adverse cardiovascular effects of smoking, there is data to suggest that CO from cigarette smoke may be an unlikely cause for atherosclerosis or thrombosis [24]. In healthy persons, CO in concentrations similar to cigarette smoking does not affect blood pressure, plasma catecholamines, platelet aggregation, or serum C-reactive protein [25]. However, CO exposure in patients with CAD can result in significant adverse effects, including lower thresholds for exercise-induced ischemia, ventricular dysfunction, and increased ventricular arrhythmias [26].

Oxidant gases. Free radical-mediated oxidative stress may play a central role in the development of atherosclerosis. In a setting of cigarette smoking, free radicals could arise from: (1) the vapor or particulate phases of cigarette smoke; (2) circulating or in situ-activated macrophages and neutrophils; and/or (3) endogenous sources of reactive oxygen species such as uncoupled endothelial nitric oxide synthase, xanthine oxidase, and the mitochondrial electron transport chain [16]. Oxidizing chemicals, including oxides of nitrogen and many free radicals, present in high levels in cigarette smoke are the prime mediators of endothelial dysfunction in smokers. Smokers are known to have lower plasma levels of antioxidants such as vitamin C and beta-carotene [27,28]. There is some evidence to suggest that administration of antioxidants such as vitamin C may improve endothelial dysfunction in chronic smokers [29].

Apart from these, cigarette smoke contains a number of metals, including aluminum, cadmium, copper, lead, mercury, nickel, and zinc, which catalyze the oxidation of cellular proteins and may lead to structural cellular damage and endothelial dysfunction. Acrolein, a reactive aldehyde produced by endogenous lipid peroxidation, is present in high levels in cigarette smoke. It adversely modifies apolipoprotein A-1 [30], the major protein in high-density lipoprotein (HDL), and leads to oxidation of prominent cellular antioxidant proteins called thioredoxins in endothelial cells, which can lead to endothelial cell death and dysfunction [31]. Polycyclic aromatic hydrocarbons found in the tar fraction of cigarette smoke are reported to
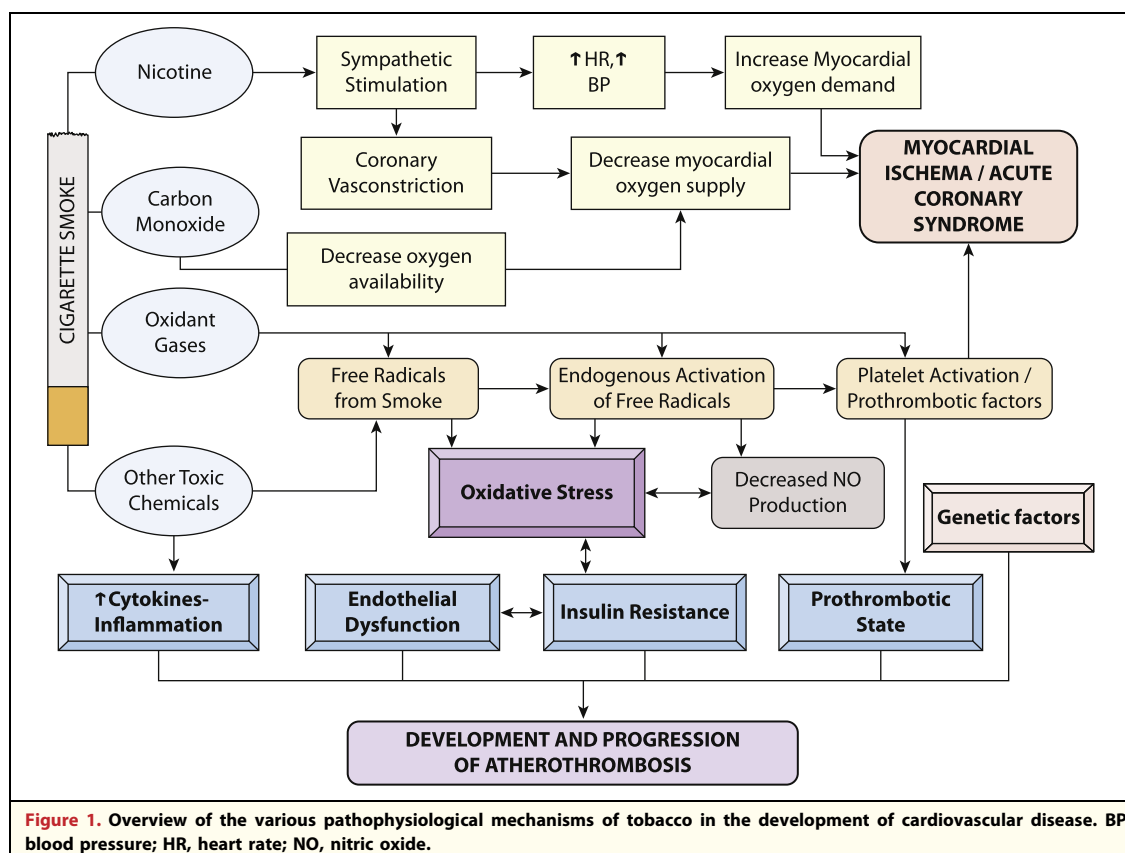
Figure 1. Overview of the various pathophysiological mechanisms of tobacco in the development of cardiovascular disease. BP, blood pressure; HR, heart rate; NO, nitric oxide.

accelerate atherosclerosis in experimental animals [32].

PATHOPHYSIOLOGIC MECHANISMS OF TOBACCO SMOKE IN CARDIOVASCULAR DISEASE

Epidemiological studies have conclusively proven the relationship between smoking and CAD. The pathobiologic mechanisms behind this link, however, are not clearly understood. Tobacco affects several known pathophysiological pathways leading to the development of atherothrombosis (Fig. 1).
Vascular and endothelial dysfunction. Smoking can damage the vascular wall, leading to impaired prostacyclin production and enhanced platelet-vessel wall interactions [33]. This can reduce the elastic properties of the aorta, resulting in stiffening and trauma to the wall [34]. Smoking, including secondhand smoke, impairs endothelium-dependent vasodilation of normal coronary arteries and reduces coronary flow reserve [35,36]. Smoking is also a risk factor for coronary vasospasm [37].

The effect on endothelial function results primarily from oxidative chemicals with enhanced oxidation of low-density lipoprotein (LDL) and reduced generation of nitric oxide [38–40].
Inflammation. Inflammation plays a major role in the pathogenesis of atherosclerosis. Cigarette smoking is associated with evidence of chronic inflammation. Studies have shown that smoking causes a 20–25% increase in the peripheral blood leukocyte count [15] and an increased level of multiple inflammatory markers including interleukin-6, C-reactive protein, and tumor necrosis factor alpha [41,42]. Elevations of various proinflammatory cytokines increase leukocyte–endothelial cell interaction leading to leukocyte recruitment, which is an early event in atherosclerosis [16]. Indeed, soluble vascular cell adhesion molecule 1, intracellular adhesion molecule 1, and E-selectin levels have been found to be higher in smokers [43]. The Northwick Park Heart Study and MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) study demonstrated elevated serum fibrinogen levels, an acute phase reactant, in smokers that reached normal levels within 5 years

of cessation [44,45]. Using data from 15,489 individuals who participated in the NHANES III (Third National Health and Nutrition Examination Survey), Bakhru and Erlinger [46] demonstrated that inflammatory markers, including C-reactive protein, fibrinogen, white cell count, and albumin, demonstrated a dose-dependent and temporal relationship to smoking and smoking cessation [46]. In their study, these inflammatory markers returned to baseline levels 5 years after smoking cessation, suggesting that the inflammatory component of cardiovascular disease resulting from smoking may be reversible with reduced tobacco exposure and smoking cessation.

Prothrombotic state. Cigarette smoking is well known to induce a prothrombotic state, as exemplified by higher rates of acute myocardial infarction and sudden death as compared to angina pectoris, in smokers [31,47]. Smoking exerts a prothrombotic state through several pathogenic mechanisms including alteration of thrombotic factors, fibrinolytic factors, and platelet-mediated pathways.

Cigarette smoking leads to elevations in fibrinogen concentration [48] and increased expression of tissue factor [49]. It induces alteration of fibrinolysis by inhibition of tissue plasminogen activator release from the endothelium and increase in plasminogen activator inhibitor-1 levels [50]. Additionally, platelet-mediated pathways of thrombosis are also activated, with platelets isolated from chronic smokers having an increased propensity to stimulated as well as spontaneous aggregation [51,52]. Smoking is associated with increased platelet-dependent thrombin generation [53]. Cigarette smoking may decrease the availability of platelet-derived nitric oxide and decrease platelet sensitivity to exogenous nitric oxide, leading to increased activation and adhesion [54,55]. Carbon monoxide-induced relative hypoxemia leads to higher red cell mass, causing increase in blood viscosity, which also predisposes to thrombosis.

Effect on lipid profile. Compared with nonsmokers, smokers have been found to have higher levels of serum cholesterol, triglycerides, very low-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), and lower serum concentrations of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-1 [56]. A recent randomized trial revealed that smoking cessation improved total HDL, and large HDL particles, but did not affect LDL-C levels or LDL size [57]. Several studies have shown that cigarette smoking enhances oxidative modification of plasma LDL-C, which may be proatherogenic and has been shown to impair endothelial function [58–60].

Smoking and insulin-resistance/metabolic syndrome. Compared to nonsmokers, smokers have been demonstrated to be more insulin-resistant and hyperinsulinemic [61]. Cigarette smoking is a risk factor for the development of type-2 diabetes [62]. This increased risk declines after smoking cessation. Smokers, compared with nonsmokers, with diabetes have higher hemoglobin A1C levels, require more insulin, and have increased risk of microvascular and macrovascular complications of diabetes. Smoking by enhancing insulin resistance, central obesity, and dyslipidemia increases the risk of incident metabolic syndrome [63]. There is increasing evidence that smoking causes greater accumulation of visceral fat. Several cross-sectional studies indicate that waist/hip ratio is higher in smokers than in nonsmokers [64,65]. Waist/hip ratio is positively associated with the number of pack-years of smoking, and there is a dose–response relation between waist/hip ratio and the number of cigarettes smoked [66].

The mechanistic link between cigarette smoking and insulin resistance is not fully established, but there is evidence for a role of nicotine. Activation of the sympathetic nervous system and release of corticosteroids and growth hormone by nicotine may contribute to insulin resistance. Insulin resistance has been shown to adversely alter lipid profile [67,68], cause endothelial dysfunction, and increase oxidative stress [69], leading to the development of cardiovascular disease.

Genetic factors. Genes have been shown to influence smoking behavior, affect the metabolism of nicotine and specific chemicals produced during combustion, and enhance (or diminish) pathomechanistic pathways associated with the atherogenic potential of smoking, including oxidative stress, its inflammatory burden, or procoagulant potential [70]. Studies have shown the interaction between heavy smoking and glutathione-*S*-transferase theta genotype GSTT1-1 and its relation to pre-clinical atherosclerosis in the form of increased intima-media thickness [71]. Recently, it was shown that the *CYBA* gene A640G polymorphism might influence individual predispositions to CAD through interactions with smoking and hypercholesterolemia [72,73]. Although several candidate genes and their genetic variants have been associated with atherosclerosis and cigarette

smoking, definite conclusions regarding causation and association cannot be made.

NONCIGARETTE TOBACCO PRODUCTS

Smokeless tobacco. Smokeless tobacco products consist of tobacco or a tobacco blend that is chewed or sucked on rather than smoked, the main types being chewing tobacco and snuff [74]. Smokeless tobacco consistently produces levels of nicotine higher than those seen with smoking [75]. Acute cardiovascular effects, similar to those caused by cigarette smoking, are seen with the use of smokeless tobacco, including coronary vasoconstriction and increase in heart rate and cardiac output [76]. Smokeless tobacco extract has been shown to be more toxic in vitro than pure nicotine and to increase oxidative stress as a result of reactive oxygen free radicals [77]. However, there is conflicting evidence from prospective and case–control studies about cardiovascular mortality or myocardial infarction caused by smokeless tobacco use. The INTERHEART (A Study of Risk Factors for First Myocardial Infarction in 52 Countries and Over 27,000 Subjects) showed that there was an increased risk of nonfatal myocardial infarctions among tobacco chewers, though relatively lesser than for smokers [78]. The INTERHEART investigators also found that the highest increase in risk of acute myocardial infarction was in smokers who also chewed tobacco.

Smoked tobacco products. Smoked noncigarette forms of tobacco such as bidis, pipes, cigars, and waterpipes are quite popular in some parts of the world. They are often mistakenly perceived as less hazardous than cigarettes, when in fact their health risks are similar [79]. Pipe and cigar smokers, compared with nonsmokers, have been shown to have a significantly high risk of major coronary events [80]. In fact, cigar smoke contains higher concentrations of toxic and carcinogenic compounds than cigarettes do [81]. Bidi smoking, common in the Indian subcontinent, delivers three times the amount of carbon monoxide and nicotine and five times the amount of tar as cigarette smoke does [82]. The few studies that have looked at the cardiovascular effects of bidi smoking reveal that bidi smokers have an increased risk of CAD [83,84]. Data on waterpipe smoking and its cardiovascular effects are limited.

"Light" cigarettes, owing to the lower nicotine and tar content, would be believed to be less harmful than smoking regular cigarettes. However, studies have shown that smoking "light" cigarettes impairs the coronary flow velocity reserve as severely as smoking regular cigarettes does [85].

SECONDHAND SMOKE

Exposure to secondhand smoke (environmental tobacco smoke, passive smoking) has been shown to pose a similar health risk as that caused by direct smoking. Approximately 40,000 deaths from heart disease are estimated to be due to exposure to secondhand smoke each year in the United States [86], reflecting the increased risk in nonsmokers of death due to CAD by approximately 20% in large epidemiologic studies [87]. The U.S. Surgeon General, in the 2006 report, estimated that living or working in a place where smoking is permitted increases the nonsmokers' risk of developing CAD by 25–30% and lung cancer by 20–30% [12]. In fact, legislations banning smoking in public places have been shown to significantly decrease the incidence of admissions of myocardial infarction [88]. Pell et al. [89] demonstrated that smoke-free legislation decreased the number of acute coronary syndromes in Scotland, and 67% of this decrease involved nonsmokers. It has been shown that exposure to secondhand smoke in healthy young volunteers compromises coronary artery endothelial function in a manner that is indistinguishable from that of active smokers, suggesting that endothelial dysfunction may be an important mechanism by which secondhand smoke increases CAD risk [90].

THIRDHAND SMOKE

The term "thirdhand smoke" has been recently coined to identify the residual tobacco smoke contamination that remains after the cigarette is extinguished and secondhand smoke has cleared from the air [91,92]. It refers to the concept of contamination of surfaces by components of tobacco smoke. Among the substances in thirdhand smoke are hydrogen cyanide, butane, toluene, arsenic, lead, carbon monoxide, and polonium-210, most of which may have carcinogenic potential. Preliminary research suggests that by-products of thirdhand smoke may pose a health risk [93], though the magnitude of risk and effect on cardiovascular system, if any, remains unknown.

CONCLUSIONS

Cigarette smoking is a leading preventable risk factor for the development and progression of cardiovascular disease. Tobacco exerts its deleterious cardiovascular effects through multiple mechanisms. Endothelial dysfunction, increased oxidative stress, and induction of a hypercoagulable state appear to be the key pathobiologic mechanisms involved. Apart from direct smoking, secondhand smoke has also been proven to be causally associated with an increased risk of CAD among nonsmokers. Clinical and experimental studies have shown that the cardiovascular risk posed by smoking reverses after smoking cessation. This emphasizes the importance of a comprehensive antitobacco campaign, comprising individual-based behavioral and pharmacological interventions to fight nicotine addiction and community-level measures, as an important public health intervention.

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