Cigarette Smoking and Cardiovascular Health

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Introduction

In their pathogenesis, cardiovascular diseases (CVDs) are among the most complex human diseases. The interplay of genes, lifestyle, and the environment defines the onset, mode of initiation, location and type of cardiovascular outcome. The myriads of risk factors, physiochemical interactions, cell types, and biological processes involved add to the complexity of these diseases (1-4).). In the 1960s, the US Surgeon General and American Heart Association issued reports warning of the dangers of smoking on fatal coronary artery disease (5-7). Since those early publications, 32 US Surgeon General reports have been released exposing the harmful effects of cigarette smoking on cardiovascular health (8,9). The 1983 Surgeon General's Report (10) was devoted entirely to cardiovascular disease. It concluded that cigarette smoking is one of the three major independent risk factors for heart disease. It also concluded that the magnitude of the risk associated with cigarette smoking is similar to that associated with the other two major heart disease risk factors, hypertension and hypercholesterolemia. CVDs caused by cigarette smoke are mediated through multiple interrelated mechanisms, including increased oxidative stress, endothelial injury and dysfunction, altered blood coagulation, and derangements of lipid composition and metabolism (11); all leading to the principal pathophysiological mechanism of coronary thrombosis and atherosclerosis (12). This article serves to provide a brief summary of the current literature on the mechanisms by which cigarette smoke causes CVDs.

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Patho-physiological Effects of Cigarette Smoking

Effects on endothelium

Endothelial cells maintain a delicate balance between (a) vasodilating (NO, prostacyclin [PGI2]) and vasoconstricting (endothelin-1) factors; (b) thrombotic (tissue Factor) and antithrombotic (tissue factor pathway inhibitor-1 [TFPI-1] and thrombin activatable fibrinolysis inhibitor) factors; as well as, (c) fibrinolytic (tissue-plasminogen activator [t-PA]) and antifibrinolytic factors (plasminogen activator inhibitor-1 [PAI-1]) (13-15). Nitric Oxide (NO) and PGI2 have direct antithrombogenic effects because they inhibit platelet activation and aggregation by a cGMP-dependent mechanism (13-15). It has been demonstrated that exposure to cigarette smoke decreases NO by altering the expression and activity of the endothelial NO synthase enzyme (16,17). It is proposed that decreases in endothelial derived NO occur via two mechanisms. First is via decreasing the bioavailability of NO by scavenging activity of free radicals derived from cigarette smoke (18,19). Second, cigarette smoke exposure alters endothelial NO synthase protein and its activity, thereby decreasing NO availability (16,17). Since NO helps regulate inflammation, leukocyte adhesion, platelet activation, and thrombosis; an alteration in NO biosynthesis would cause both primary and secondary effects on the initiation and progression of thrombotic events and contributing to all stages of atherosclerotic plaque formation (13,14).

Proinflammatory effects

Cigarette smoke has been found to be associated with increased levels of multiple inflammatory markers, including peripheral leukocytosis, C-reactive protein, homocysteine, interleukin-6, and tumor necrosis factor-α (20-22). Inflammation is known to constitute an essential element in atherogenesis. Smokers were shown to have significantly elevated white blood cell counts, which was tightly correlated to the formation of carotid atherosclerotic plaques (23). Lavi et al (24) reported

increased levels of neutrophils, lymphocytes, and monocytes in smokers when compared with nonsmokers in patients with chest pain and early coronary artery disease. These systemic immunologic alterations were found to correlate with local processes within the atherosclerotic plaque, characterized by inflammation and increased expression of matrix metalloproteinases (25).

Lipid modification

Effects of cigarette smoke on lipids have also been extensively studied. Earlier studies by Craig et al (26) demonstrated that cigarette smoke quantitatively affects lipid profiles by finding a statistically significant correlation between smoking and increased total serum cholesterol, very–low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and triglyceride (TG) serum concentrations. They also found HDL and Apolipoprotein A1 levels to be decreased in smokers, in a dose-dependent manner. Subsequent studies reinforced that smoking modifies serum lipid profiles in a proatherogenic manner (27,28).

Increased oxidative stress

Free radicals and oxidants present in cigarette smoke, combined with endogenously produced oxidants and radicals cause a pro-oxidative environment leading to in vivo oxidative stress (29). This oxidative stress is shown to change lipids qualitatively demonstrated by reported increased presence of lipid peroxidation products in the serum of smokers (30), and by increased levels of circulating autoantibodies against oxidized LDL (31). It is suggested that peroxynitrite (generated by a reaction between NO and superoxide anion) is involved in the impairment of in vivo antioxidant systems leading to the oxidative modification of LDL in smokers' blood (32-34). Since only oxidatively modified LDLs are taken up by macrophages and transformed into foam cells, it is implicated that in vivo the oxidation of lipids is another way by which smoking induces and accelerates atherosclerosis.

Effects of Cigarette Smoke on Vascular Structure and Function

In view of the diagnostic, prognostic and therapeutic significance of endothelial function and arterial stiffness, a number of non-invasive techniques have been introduced for their assessment. These include flow-mediated dilation (FMD), finger plethysmography (RH-PAT), digital thermal monitoring (DTM), pulse wave analysis (PWA), pulse wave velocity (PWV), pulse contour analysis (PCA) and carotid wall distensibility coefficient (DC), carotid intima-media thickness (cIMT) (35-40) and ankle brachial index (ABI) (41,42). Kasliwal et al demonstrated the role of brachial artery FMD for detecting subclinical atherosclerosis (43) and its association with coronary artery disease (44) in the Indian population. The role of cIMT as a predictor of CAD in Indians has also been well-established (45-47).

The relationship between FMD and IMT has also been studied to some detail, but the results are inconsistent (48). In The Cardiovascular Risk in Young Finns study (49) brachial FMD was inversely associated with cIMT in a multivariate model adjusted for age, sex, brachial vessel size, and several other risk variables. When comparing brachial FMD and cIMT to Framingham Risk Scores (FRS) in African Americans (50), significant inverse relation between FMD and FRS was found, but IMT was not statistically different among the risk groups. However, in a study comparing FMD, CFVR and IMT to the Framingham Risk Score in patients without clinical atherosclerosis, IMT correlated best with the Framingham score (51). Within Indian subsets, similar inverse correlation of cIMT and brachial FMD was found in diabetic patients (52) along with significant correlation between cIMT and brachial-ankle PWV in patients with coronary artery disease but no correlation in individuals without major atherosclerotic vascular disease (53).

Effects of smoking on FMD

A landmark study in 1993 by Celermajer et al (54) showed that continuous smoking impairs brachial FMD in a dose-dependent manner in healthy young adults. FMD was observed in all the control subjects (10 ± 33%; range 4% to 22%) but was impaired or absent in the smokers (4 ± 3.9%; range 0% to 17%; $P<0.0001$). FMD in the smokers was inversely related to lifetime dose smoked (6.6 ± 4.0% in very light smokers, 4.0 ± 3.1% in light smokers, 3.2 ± 3.2% in moderate smokers, and 2.6 ± 1.2% in heavy smokers; $P<0.01$).

Zeiher et al (55) showed that long-term cigarette smoking is independently associated with impaired endothelium-dependent coronary vasodilation with a reduced flow-dependent dilator response of epicardial arteries regardless of the presence or absence of coronary atherosclerotic lesions. Since then, numerous studies

have evaluated the effect of cigarette smoke FMD with similar results (56-60).

Effects of smoking on cIMT

Two of the earliest population-based studies linking cigarette smoke exposure to decreased cIMT were both published in 1994. The Cardiovascular Health Study (61) found that increased smoking (current smokers>former smokers>never-smokers) led to significantly greater internal and common carotid wall thickening and internal carotid stenosis. Also, a significant dose response relation was seen with pack years of smoking: the prevalence of clinically significant (>50%) internal carotid stenosis increased from 4.4% in never-smokers to 7.3% in former smokers to 9.5% in current smokers. Similar results were published in The Atherosclerosis Risk in Communities Study (62) which confirmed that increase in exposure to cigarette smoke was significantly related to increased IMT. Subsequently, a score of studies evaluated the effects of chronic cigarette smoking on cIMT with comparable results (63-70).

Few studies also looked at acute cigarette smoke exposure. It was found that smoking even 1 cigarette caused similar effects to chronic cigarette exposure by acutely increasing cIMT, heart rate and blood pressure (71) including increased platelet dependent thrombin levels (72) leading to increased vulnerability of plaque rupture. Moreover, smokers had sustained and more intensive unfavorable effects in endothelial function than non-smokers after smoking one cigarette: endothelial dysfunction after smoking (measured by reduction in FMD), remained significant for 1 hour in smokers, but only for 30 min in non-smokers. FMD 1 hour after smoking was significantly higher in non-smokers than in smokers (73).

A recent study revealed that smoking light cigarettes impairs FMD as much as smoking regular cigarettes, arguing against light cigarettes as a less harmful alternative (74). Similarly, consumption of light cigarettes did not reduce the atherogenic effect of smoking on cIMT. No differences were found in cIMT (75) or CFVR (76) between smokers of cigarettes with high or low nicotine, tar, or carbon monoxide content strengthening the case for a dose dependence on the number of pack years smoked rather than the strength of the ingredients of the cigarette.

Effect of cigarette smoke on clinical outcomes

The effects of cigarette smoking on vascular physiology, structure and function translate directly, and correspond to clinical outcomes related to the cardiovascular system (77). Numerous studies have documented that exposure to cigarette smoke increases the risk of developing myocardial infarction multifolds (78-80). It also increases the risk of developing heart failure (81,82), number of admissions due to heart failure (83), and the duration of heart failure related hospital stay.

Cigarette smoke exposure was has also been shown to increase the risk of peripheral artery disease (84,85) including increased odds of developing abdominal aortic aneurysms (86,87). Additionally, cigarette smoking universally increases the risk for stroke in both men and women of multiple ethnicities (88).

Apart from vascular disease, cigarette smoking also increases the risk of developing new arrhythmias in a dose-dependent manner (89-92). Many large observational studies including the Rotterdam Study (93) and the ARIC Study (94) have found that the incidence of atrial fibrillation was almost twice as high in current smokers than never smokers after adjusting for other independent risk factors. The risk of ventricular tachycardia and ventricular fibrillation as assessed by number of shocks delivered by implantable cardioverter-defibrillator was also higher in smokers as compared to non-smokers (95,96). The risk of sudden cardiac death also increased dose-dependently in smokers when compared to ex-smokers or non-smokers (97).

In patients who have undergone revascularization through either PCI or CABG, continued exposure to cigarette smoke is associated with increased incidences of adverse clinical outcomes (98) including stent thrombosis (99-101) or graft occlusion (102,103), new MI and reinfarction (104-106), and increased length of hospital stay (107).

Effects of Passive Smoke

Having established through numerous studies that active cigarette smoking increases the risk of developing cardiovascular diseases multifold, the paradigm shifted to the evaluation of the effect of passive smoking. One of the first reports indicating the detrimental effects

of passive smoking was published in 1986 by the US Surgeon General (108,109). Further research has shown that the mechanisms by which passive smoking affects the cardiovascular system is the same as active smoking, which includes endothelial dysfunction, increased oxidative stress, lipid modification, platelet activation and a pro-inflammatory state (110). Individuals are exposed to 2 types of passive smoking: second hand smoke (SHS) and environmental tobacco smoke (ETS). In a review of 10 published epidemiological studies, it was found that ETS affected the cardiovascular system in the same was as active smoking did (111).

SHS has two main components: sidestream and mainstream smoke. Sidestream smoke emerges from the tip of a burning cigarette and accounts for 85% of the total amount of SHS. The remaining 15% is made up of mainstream smoke, which has been inhaled and is exhaled by an active smoker (112,113). The concentration of numerous toxins has been shown to be dramatically (up to 100-fold) elevated in sidestream smoke when compared with mainstream smoke. Additionally, the particles in sidestream smoke are smaller than those in mainstream smoke, allowing them to be deeply inhaled in the lungs and underscoring the potential adverse impact of SHS on health (114).

A large meta-analysis (115) of 18 studies found that nonsmokers exposed to environmental smoke had a relative risk of coronary heart disease of 1.25 ($P<0.001$) as compared with nonsmokers not exposed to smoke. Passive smoking was consistently associated with an increased relative risk of coronary heart disease in both cohort and case–control studies, irrespective of gender or exposure at home or work. A significant dose–response relation was identified, with respective relative risks of 1.23 and 1.31 for non- smokers who were exposed to the smoke of 1 to 19 cigarettes per day and those who were exposed to the smoke of 20 or more cigarettes per day, as compared with nonsmokers not exposed to smoke.
Many studies also evaluated the effect of exposure to passive smoking in childhood to the risk of cardiovascular diseases in adulthood (116-118). The most notable results were published by West et al in The Cardiovascular Risk in Young Finns Study (119) where during a 26 year follow-up period, it was found that childhood exposure to passive smoking was associated with carotid atherosclerotic plaque in young adults. Again, the risk was dose dependent; children living in households where both parents smoked were at higher risk when compared to households where only one parent smoked.

Benefits of Smoking Cessation

Though cigarette smoke exposure leads to detrimental effects on the human body and especially on the cardiovascular system, it was found that these effects could potentially be reversed through smoking cessation (33,58,110). Improvements in both FMD and cIMT values were found in as little as 1 year post smoking cessation in active smokers (22,41,56,112,118). A meta-analysis of 20 studies showed a 36% reduction in the crude relative risk of mortality for patients with coronary heart disease who quit smoking compared with those who continued smoking. Smoking cessation also leads to an exponential reduction in acute cardiovascular events, particularly in the first year after quitting (120).
A notable effect of smoking cessation was seen on second hand smoke. It was noted in various cities across the globe that public smoking bans resulted in fewer hospitalizations due to cardiovascular events including acute myocardial infarction and stroke (121-123). Some of these results were apparent in as little as 6 months after enforcement of the ban legislature (124). Several meta-analyses have also been conducted to support the relation between decline in acute cardiac events and implementation of smoking ban legislature (125-127). A recent meta-analysis concluded that public smoking bans reduced hospital admissions due to various conditions not only limited to cardiovascular events. These included reduced hospital admissions due to causes like acute coronary events (including acute myocardial infarction, acute coronary syndrome, angina and ischemic heart disease), sudden cardiac death, stroke, transient ischemic attack, chronic obstructive pulmonary disease, asthma, lung infections, and spontaneous pneumothorax (128). The study also concluded that more comprehensive laws were associated with greater reductions in risk.

Conclusion

Smoking kills 6 million humans per year, with ≈10% of these deaths related to secondhand smoking. Smoking is responsible for an alarming but preventable 10% of CVDs (129). New research suggests that the effects of passive smoking are largely underestimated and these effects might be as large as active smoking itself (130). Cigarette smoke consists of more than 4000 different chemicals, most of which have not been identified or investigated. Consequently, the mechanisms by

which cigarette smoke affects cardiovascular functions are still poorly understood. Smoking plays a strong role not only in CVD initiation but also significantly contributes to and causes disease progression and fatal cardiovascular outcomes. Therefore, smoking cessation still remains the cornerstone of the strategy to reduce the mortality and morbidity associated with smoking. It has been demonstrated through various studies that cessation of smoking not only benefits the smoker, but also that smoke-free laws are followed by fewer hospitalizations and lower healthcare expenditures for a wide range of diseases and that comprehensive laws ending smoking in workplaces, restaurants, and bars are associated with greater effects. The general public, health professionals, and policy makers should consider these positive associations as they develop smoking cessation programs.

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