IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
October 2016 Vol.:7, Issue:3

Pathophysiological Effects of Smoking on Cardiovascular System and Function: The Role of Nicotine and Carbon Monoxide and the Benefits of Smoking Cessation

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Submission: 7 October 2016
Accepted: 12 October 2016
Published: 25 October 2016

Keywords: Cardiovascular disease, Risk factors, Smoking, Sedentary behavior, Aortic aneurysm, Endothelial dysfunction, Nicotine, Carbon monoxide

ABSTRACT

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide.The global tobacco epidemic contributed to 100 million deaths worldwide during the 20th century and continues to kill nearly 6 million persons each year, including approximately 600,000 from second hand smoke. Potential relationship exists between smoking and CVD and is of great public health importance. The primary cause of CVD is a combination of several risk factors (RFs) that correlate with the progression of endothelial injury and the development of atherosclerosis. The number of deaths associated with cardiovascular events is escalating in many countries condition is widely attributable to unhealthy outcomes in its association with risk factors such as smoking and sedentary behavior. Tobacco use is a principal contributor to the development of heart attacks, strokes, sudden death, heart failure, aortic aneurysm and peripheral vascular disease. Smoking is a major risk factor for cardiovascular morbidity and mortality and is considered to be the leading preventable cause of death in the world. Cigarette smoke contains more than 5000 chemical substances, including nicotine and carbon monoxide (CO) that can have harmful effects on cardiovascular function. These basic ingredients of tobacco smoke cause an increase in oxidative stress, endothelial damage/dysfunction and are associated with significantly higher serum concentrations of total cholesterol and triglycerides, insulin resistance, hemodynamic alterations, hypercoagulable state and lower levels of the cardioprotective high-density lipoprotein. By causing intravascular inflammation, smoking promotes the development of atherosclerosis and cardiovascular disease. The purpose of this article is to provide a brief description of the effects of smoking, and in particular, the effects of nicotine and CO, on cardiovascular function. Nicotine deregulates cardiac autonomic function, boosts sympathetic activity and increases heart rate (HR) at rest while blunting HR elevation during progressive exercise and lowering the maximum HR that can be achieved. At the same time, the smoking generated CO binds with hemoglobin and myoglobin, reduces arterial O_2 blood saturation, compromises the efficiency of respiratory enzymes, and causes dysfunction of the O_2 production, transportation and delivery system, especially during exercise, substantially reducing the functional capacity and the performance of the circulatory system. All of these act synergistically as pathobiologic mechanisms of atherothrombosis in tobacco users.

INTRODUCTION

Cardiovascular disorders (CVD) are the group of disorders that involves the heart and blood vessels. Cardiovascular diseases are the leading cause of death globally[1]. The death caused by CAD (coronary artery disease) is responsible for approximately half of all deaths from CVD[2]. Deaths from CVD are more common and largely the product of interactions among the modifiable risk factors that are escalating in abundant of the developing world whereas rates have declined in most of the developed countries[1].

Cigarette smoking is one amongst the foremost necessary important modifiable risk factors for cardiovascular disease[3]. In smokers with established CVD, quitting or smoking cessation reduces mortality more than any other secondary prevention measure which conjointly includes the use of statins and aspirin[4].However, nicotine dependence is a powerful substance use disorder[5]. Behavioral risk factors are responsible for 80% of all diagnoses of coronary heart disease and cerebrovascular disease[6]. Although unhealthy diet, physical inactivity and harmful use of alcohol play a role; by far the leading behavioral risk factor of cardiovascular disease is smoking. Smoking has been attributed to account for 14% of deaths from heart and circulatory disease[7]; with the risk being substantially reduced within two years of smoking cessation[8]. Compared with non-smokers, smokers have a chance of 2 to 4 times increased risk of heart disease and of stroke[9]. The World Health Organization predicts an outstanding increase in the prevalence over successive10-20 years, with an increase from 17 million losses to life in the world attributable to CVD in 2008 to 23.4 million by 2030 [6].

Smoking still remains an important public health issue and a significant contributor to cardiovascular disease-related morbidity and mortality[10]. Smoking is calculable to cause 10% of cardiovascular diseases and is the second leading cause of CVD, after hypertension. The influence of tobacco smoke is not confined exclusively to smokers. Almost 6 million people die every year from tobacco use or exposure to second-hand smoke, accounting for 6 % of female and 12 % of male deaths worldwide. However, Smoking is avoidable and advancing a tobacco-free world is a key strategic priority for the World Heart Federation[11]. The awareness of links between smoking and CVD remains low in many parts of the world. The risk of stroke is extremely high in china and more than 70 % of all smokers do not know that smoking increases their risks of having a stroke[12].

Internationally, 25% of middle-aged cardiovascular deaths were mainly attributable to smoking[13]. The European Society of Cardiology has recently reported that smoking causes 28% of cardiovascular deaths in men between the age 35 to 69 years and 13% in women of the same age[14]. Based on estimates by the WHO, each year tobacco continues to kill nearly 6 million people—which includes more than 600,000 passive smokers—through heart disease, lung carcinoma and other illnesses. If current trends continue, the death toll is projected to reach more

than 8 million per year by 2030 [15]. Smoking ranks among the top causes of cardiovascular disease, including ischemic stroke, coronary heart disease, peripheral artery disease and abdominal aortic aneurysm (Figure No.1)[14]. It is also associated with an increased risk of certain types of cancer and is a major cause of chronic obstructive pulmonary disease[15, 16]. Smoking, either actively or passively, can cause cardiovascular disease via a series of interdependent processes, such as enhanced oxidative stress, autonomic and hemodynamic alterations, endothelial dysfunction, inflammation, hyperlipidemia, thrombosis or other effects[17]. Cigarette smoke contains more than 5000 chemical substances that have potentially harmful effects/actions on cardiovascular system and function[18]. These include nicotine, carbon monoxide (CO), carbon disulfide, oxidative gases, butadiene, polycyclic aromatic hydrocarbons, carbonyls, benzene and minerals. Although most of the toxic substances present in tobacco smoke are mainly the generic products of the combustion of organic materials, exposure to smoking involves contact with 2 substances that are mainly specific to the tobacco smoke and are known to be damaging or harmful to the health: Nicotine and CO[19].

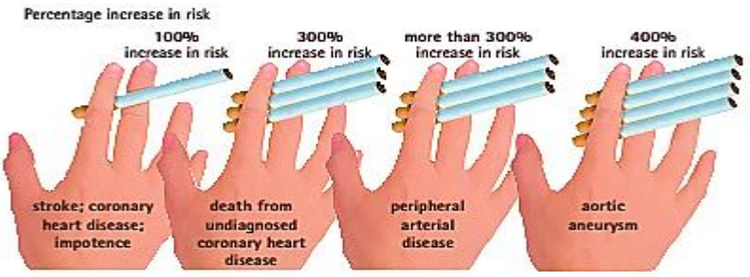

Figure No.1 Cardiovascular risks of smoking

PHYSICAL AND BIOCHEMICAL PROPERTIES OF CIGARETTE SMOKE:

Conventionally, cigarette smoke is principally divided into two phases: a tar phase and a gas phase. The tar also called particulate phase is mainly defined as the material that is trapped when the smoke stream is undergone through the Cambridge glass-fiber filter that retains 99.9% of all particulate material with a size >0.1µm. The gas part is the material that passes through the filter. Primarily the particulate phase of cigarette smoke contains >1017 free radicals/gram, and the gas phase contains >1015 free radicals/puff[20]. The radicals associated with the tar phase are long-lived (hours to months), whereas the radicals related with the gas phase have somewhat shorter lifespan (seconds) [20, 21, 22]. Cigarette smoke that is primarily drawn through the tobacco through the cigarette into mouth of an active smoker's is known as mainstream smoke. Sidestream cigarette smoke is the smoke that is emitted from the burning ends of a cigarette. Mainstream cigarette smoke comprises 8% of tar and 92% of volatilized components[20].

Environmental tobacco smoke results from the combination of side-stream smoke (85%) and a minor fraction of exhaled mainstream smoke (15%) from smokers[23]. Sidestream cigarette smoke contains a comparative concentration of the toxic gaseous component than mainstream cigarette

smoke[24]. Of all the known constituents of tobacco smoke, nicotine, a component of the tar phase, is the main addictive substance of cigarette smoke[25].

SUBSTANCES IN TOBACCO SMOKE AND THEIR ABSORPTION:

The 2 substances absorbed in any appreciable amounts from tobacco smoke are carbon monoxide and nicotine. The standard cigarette approximately weighs 1 gram and contains 20 mg of nicotine. In line with Baumberger, when a cigarette is smoked, 35% of the nicotine is destroyed at the burning tip, 35% is lost in the facet stream and much of this is given off to the environment, 22% enters the mouth through the mainstream of the smoke and remaining 8% remains in the unsmoked portion of the cigarette. It is calculable that 3 to 4 mg. of nicotine enters the respiratory passages while from 2.5 to 3 mg. is absorbed by the lungs. When the smoke is held in the mouth for 2 seconds and then released, 66% to 77% of the nicotine is absorbed, and when smoke is indrawn, 88% to 98% of the nicotine is absorbed. Thus the amount of nicotine absorbed depends on the period of smoke that continues to be within the mouth, whether or not the smoke is indrawn or not, and therefore the frequency and depth of inhalation[26].

This article examines the relationship between smoking and CVD. It explains the mechanisms by which smoking causes smoking causes cardiovascular damage, the clinical effects of smoking and the health benefits of quitting smoking. Today one of the predominate medical question is, "Does smoking extremely have a sway on the cardiovascular system of man? “It seemed wise to review the proof bestowed on this question throughout the last decade and to refer briefly to earlier work whenever necessary. The purpose of this article is to provide a brief description of the effects of smoking, and in particular, the potentially harmful effects of nicotine and CO, on cardiovascular function, providing essential information that could contribute to reducing the smoking epidemic and its consequences for cardiovascular health. This paper also outlines the various postulated pathophysiological mechanisms concerned in tobacco-related cardiovascular disease.

ROLE OF VARIOUS COMPONENTS OF TOBACCO SMOKE IN CARDIOVASCULAR DISEASE:

The constituents of cigarette smoke that have received the best attention, as potential contributors to cardiovascular disease are nicotine, carbon monoxide and oxidant gases. There has conjointly been some analysis on polycyclic aromatic hydrocarbons smoke which will contribute to pathology atherogenesis[27].

NICOTINE:

Nicotine is classed as an alkaloid (like morphine and cocaine) and meets the criteria of an extremely addictive drug. One cigarette delivers 1.2-2.9 mg of nicotine, and therefore the typical

one pack per day smoker absorbs 20-40 mg of nicotine each day[28]. Nicotine, one in all the foremost studied constituents of cigarette smoke, is a potent ganglionic and CNS stimulant. Each puff contains approximately 50μg of nicotine. Nicotine exerts its cardiovascular effect via sympathetic neural stimulation[29, 30].

The hemodynamic effects of cigarette smoking are mediated primarily by the effects of nicotine. Nicotine predominantly accelerates heart rate, blood pressure and flow and cardiac output, leading to an increase in myocardial oxygen demand. It rises heart rate both mildly (up to 10–15 beats/min), as well as throughout the day with regular dosing (average rise of 7 beats/min as measured on ambulatory monitoring) [27]. As an addictive drug, nicotine has 2 very important potent effects: it is a stimulant and it's conjointly a depressant[31]. Nicotine causes deregulation of cardiac autonomic function, boosts sympathetic activation, raises pulse rate, causes coronary and peripheral vasoconstriction, increases myocardial workload of heart, and stimulates adrenal and neuronal catecholamine release. Additionally, nicotine is associated with endocrine insulin resistance, increased serum lipid levels, and intravascular inflammation that contribute to the development of atherosclerosis[32].

CARBON MONOXIDE:

Carbon monoxide (CO) is indrawn in cigarette smoke. Although previously thought to be responsible for the adverse cardiovascular effects of smoking, there is information to suggest that CO from cigarette smoke may be an unlikely cause for atherosclerosis or thrombosis[33]. However, CO exposure in patients with coronary artery disease (CAD) can result in significant adverse effects, including lesser thresholds for exercise-induced ischemia, ventricular dysfunction, and increased ventricular arrhythmias[34].Carbon monoxide (CO) is produced from the incomplete combustion of carbon-containing substances, such as gasoline and tobacco[35]. The amplitude of CO within the atmosphere is extremely low and has very little impact on humans. Comparatively, 3-6% CO in tobacco smoke (and the 2-3 times higher concentrations in pipe and cigar smoke) represents significantly higher levels than are normally encountered[36].

Carbon monoxide exposure has been implicated in the process of atherosclerosis, contributing to the accumulation of cholesterol in the aorta and coronary arteries[37, 38]. In addition, CO exposure enhances endothelial damage, resulting in harmful effects within the presence of ischaemic heart or peripheral vascular disease. The deleterious effects of CO are more profound within the myocardium than in peripheral tissues, because of the extremely elevated oxygen extraction by the myocardium at rest[39]. The main mechanism by which CO causes heart disease is through hypoxia. Inhalation of cigarette smoke, by either active or passive smokers, will increase the levels of carboxyhemoglobin (COHb) within the blood, decreasing the supply of O_2 to the tissues. In addition, hemoprotein **(**myoglobin) binds with CO in order that the heart muscle does not take up the mandatory O_2 and does not perform optimally. The reduced O_2 uptake as a result

of smoking, together with an increase in serum lactic acid levels (lactic acidosis), leads to a reduction in peak aerobic capacity and to a significant decrease in maximum O_2 uptake (VO_2max).

CARBONMONOXIDE AND HAEMOGLOBIN:

The potent chemical affinity between hemoglobin (Hb) and CO is well-known. It has been calculable that the affinity between Hb and CO is 200 times greater than the affinity between Hb and oxygen[36]. An immediate consequence of this distinction is that the widespread binding of Hb by CO within the blood, the creation of COHb, and a great increase in its serum levels, leading to a big decrease in oxygen uptake by peripheral tissues. More specifically, the CO in smoke binds Hb, creating COHb[39] through the subsequent reaction:

$$\mathbf{HbO_2 + CO \rightarrow COHb + O_2}$$

Where HbO_2 is oxyhaemoglobin[40]. The presence of COHb in the blood, apart from decreasing its O_2 saturation, further causes the state of particulate-induced hypoxaemia[36]. In smokers, COHb levels are 5% on average and may reach as much as 10% in heavy smokers. In distinction, in non-smokers COHb levels range between 0.5-2%, looking on their exposure to automobile exhaust[41,42].More specifically, one and a half hours after smoking, COHb levels vary on the average between 3.9-4.1%,[43] while elsewhere it has been shown that immediately after smoking COHb levels were around 9%[35]. The rise in blood COHb levels and the reduced O_2 supply to the tissues affect the vascular permeability[41]. The increase in endothelial permeableness, alongside the injuries to the intima of the arterial wall associated with exposure to CO, leads to subendothelial edema manifested by early arterial sclerosis changes, such as fat deposition in the arterial walls[44]. Finally, the presence of CO in the blood is taken into account for severe anatomical and morphological changes within the heart muscle, such as partial or total necrosis of muscle fibrils, and degenerative processes in the mitochondria. Other observations include extra and intracellular edema, capillary wall puffiness, an increase in the variety of ribosomes, and reparative fibrotic changes[45].

OXIDANT GASES:

Free radical-mediated oxidative stress might play a central role in the development of arterial sclerosis. In a setting of cigarette smoking, free radicals may arise from (1) the vapour 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 tissue nitric oxide synthase, xanthine oxidase, and the mitochondrial electron transport chain[46]. Oxidizing chemicals, including oxides of nitrogen and lots of free radicals, present in high levels in cigarette smoke are prime mediators of endothelial dysfunction in smokers. Smokers are known to have lower plasma levels of antioxidants such as vitamin C and

beta carotene[47, 48]. Apart from these, cigarette smoke contains a variety of metals, including aluminum, cadmium, copper, lead, mercury, nickel, and zinc that turn the oxidation of cellular proteins and may lead to structural cellular damage and endothelial dysfunction. Acrolein, a reactive organic compound created by peroxidation of endogenous lipid, is present in high levels in cigarette smoke. It adversely modifies Apolipoprotein A-1[49], the foremost macromolecule in high-density lipoprotein (HDL), and results in oxidation of prominent cellular antioxidant proteins called thioredoxins in endothelial cells, which might cause endothelial cell death and dysfunction[50].

PATHOPHYSIOLOGICAL MECHANISMS OF TOBACCO SMOKE IN CARDIOVASCULAR DISEASE:

Inhaling tobacco smoke causes many immediate responses inside the heart and its blood vessels. Epidemiological studies have conclusively proven the relationship between smoking and CAD. Tobacco affects several known pathophysiological pathways resulting in the event of atherothrombosis (Figure No.2).

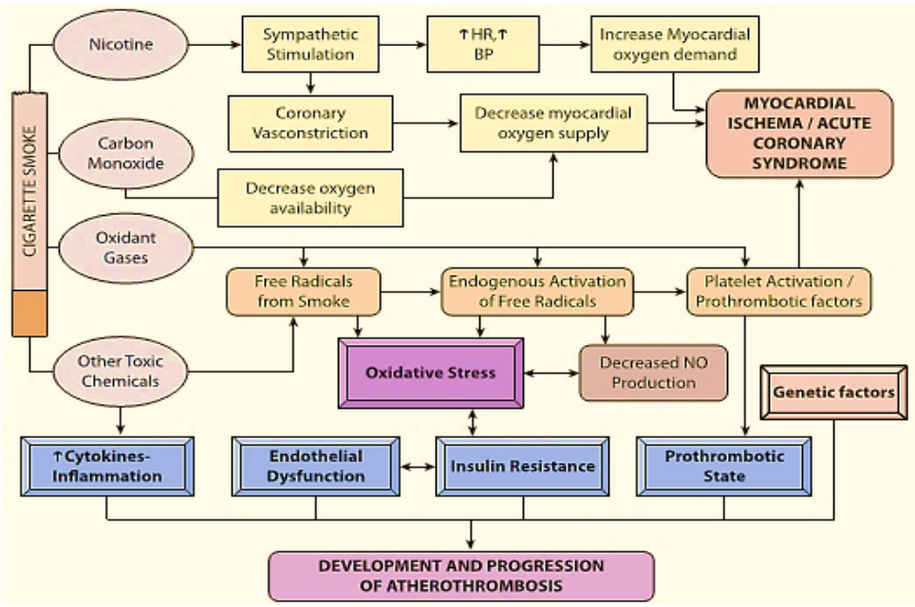

Figure No.2 Overview of the various pathophysiological mechanisms of tobacco in the development of cardiovascular disease.

BP=blood pressure; HR=Heart rate; NO=Nitric oxide.

VASCULAR AND ENDOTHELIAL DYSFUNCTION:

Chronic exposure to tobacco smoke results in a pathological alteration of endothelial function. Endothelial dysfunction may be caused by metabolic (dyslipidemia), environmental (smoking), and physical (arterial hypertension) factors, or by inflammation that successfully provokes pathological conditions. It is characterized by an imbalance between vasodilatory and vasoconstrictive substances originating from the endothelium, anticoagulant drugs and

procoagulant mechanisms, growth factors and growth inhibitors[51].Smoking can damage the vascular wall, resulting in impaired prostacyclin production and enhanced platelet-vessel wall interactions[52]. This could scale back the elastic properties of the arterial blood vessel, leading to stiffening and trauma to the wall[53]. Smoking, including secondhand smoke, impairs endothelium-dependent vasodilation of traditional coronary arteries and reduces coronary flow reserve[54, 55]. The impact on endothelial function results primarily from oxidative chemicals with enhanced oxidation of low-density lipoprotein (LDL) and reduced generation of nitric oxide[56, 57, 58].

Impairment of vasodilatory function is one of the earliest manifestations of CAD changes in a vessel. In both animal and human models, many studies have demonstrated that both active and passive cigarette smoke exposure were related to a decrease in vasodilatory function[59]. In humans, cigarette smoke exposure impaired endothelium-dependent vasodilation (EDV) in macrovascular beds such as coronary and limb arteries and in microvascular beds[60]. Nitric oxide (NO), a free radical, is primarily accountable for the vasodilatory function of the endothelium[61]. Under normal conditions, the free radicals circulating in the human body are neutralized by defensive mechanisms. However, if their concentrations within the blood ought to increase greatly because of excessive exposure to harmful factors such as smoking, then they cannot be regulated and will cause dangerous mutations that destroy cells. In these circumstances, oxidative stress is seen to arise[41]. The term "oxidative stress" refers to the total of the intracellular and extracellular conditions that cause chemical or metabolic production of reactive oxygen species (ROS) [62, 63].

Chronic exposure to tobacco conjointly weakens the antioxidant defensive mechanisms that regulate the massive numbers of smoking-induced free radicals, leading to a significant increase in oxidative stress. Oxidative stress, the oxidation of lipids, proteins, and DNA, is directly related to atherogenesis[41]. An indicative finding is that when levels of isoprostanes (indexes of lipid peroxidation and oxidative damage) were measured in smokers, their levels were found to be beyond in non-smoker[62].

The reaction of nitric oxide gas(NO) with the free radicals contained in smoke reduces NO's bioavailability, meddling with its vasodilatory, antithrombotic, anti-inflammatory, and antioxidant effects, in addition as its influence on endothelium permeability and myocardial function (reducing the diastolic pulse distensibility of the left ventricle)[64]. The alteration in biosynthesis of NO and its attenuated activity, [65] together with the smoking-induced reduction in prostacyclin production[66] and therefore the direct toxic effect of nicotine on endothelial cells that causes direct structural damage, are important factors that may lead to endothelial dysfunction[67].

Using an extract of cigarette tobacco or its isolated ingredients, such as nicotine, several in vitro studies have found that smoking is related to reduced NO availability. It has been shown that nicotine concentration in smokers' blood serum reduces the availability of NO in human

umbilical vein endothelial cells (HUVECs), as well as in human coronary artery endothelial cells, leading to a reduction in the brachial artery's endothelium-dependent vasodilation[63].Using this model, Barua *et al.* demonstrated that exposure to smokers' sera attenuated NO availability in both HUVECs and human coronary artery endothelial cells, by neutering the expression and activity of the endothelial NO synthase enzyme[65].

In addition, they noted a big correlation between flow-mediated brachial artery endothelium-dependent vasodilation and NO bioavailability from cultured HUVECs exposed to serum from the same individuals. On the opposite hand, CO, which is considerably elevated in smokers, inhibits the creation of NO and takes its place in hemoglobin bonds[68]. These findings lead to the conclusion that the large quantities of free radicals contained in smoke enhance aerobic stress and, together could result in reduced NO bioavailability, nicotine-induced vasoconstriction and impaired vasodilation, may lead to endothelial dysfunction. The consequent endothelial damage contributes to the formation and progression of fatty tissue plaque, and reduces blood flow via occlusion and vasospasm, so inflicting cardiovascular disease[69].

INFLAMMATION:

Inflammation plays a crucial role in the pathological process of coronary-artery disease. Cigarette smoking is related to proof of chronic inflammation. Several studies have already shown that smoking causes a 20–25% increase in the peripheral blood leukocyte count[70] and an increased level of multiple inflammatory markers together with interleukin-6, C-reactive protein, and tumor necrosis factor alpha[71, 72]. Elevations of varied proinflammatory cytokines increase leukocyte–endothelial cell interaction resulting in leukocyte recruitment, which is an early event in atherosclerosis[46]. Indeed, soluble vascular cell adhesion molecule 1, intracellular adhesion molecule 1, and E-selectin levels have been found to be higher in smokers[73]. The Northwick Park Heart Study and MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) study has shown elevated serum fibrinogen levels, an acute phase reactant, in smokers that reached normal levels within 5 years of cessation[74,75]. Using data from 15,489 individuals who participated in the NHANES III (Third National Health and Nutrition Examination Survey), Bakhru and Erlinger demonstrated that inflammatory markers, including white corpuscle count, C-reactive protein, fibrinogen, and albumin, demonstrated a dose-dependent and temporal relationship to smoking and smoking cessation. 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[76].

Cigarette smoking additionally causes activation of proatherogenic molecules leading to alteration in cell-cell interactions. Cigarette smoking extract exposure was associated with a 70% to 90% increase in adherence between human monocytes and HUVECs in culture attributable to

the increased expression of adhesion molecules on the surface of both monocytes and HUVECs[77]. Exposure to CSE increased by 200% the rate of transendothelial migration of monocyte-like cells across a HUVEC monolayer[78]. Monocytes isolated from smokers increased expression of the integrin CD 11b/CD 18, which augmented the adhesiveness of the monocytes to HUVECs in culture[79]. Similarly, Adams *et al*. Exposing human monocytes and HUVECs to smoker's body fluid, found a significant increase in adhesion between these cells that was related to multiplied expression of ICAM-1 on HUVECs[80].

LIPID PROFILE AND METABOLISM:

Tobacco smoke, specifically nicotine, has a vital impact on lipid metabolism and also the regulation of lipid levels within the blood[81].Therefore, cigarette smoke might promote hardening of the arteries **(**atherosclerosis), in part, via its effects on the lipid profile[63]. Smoking is related to considerably elevated blood concentrations of total cholesterol and triglycerides[81]. Additionally, various studies have shown a tendency for LDL and VLDL cholesterol to be slightly higher in smokers[82]. On the other hand, smoking lowers serum concentrations of HDL cholesterol, a robust protective factor against the event of atherosclerosis[83, 84].The distinction is sometimes tiny, 5 mg/dl or less, but this distinction represents a 10% decrease and would be expected to affect atherogenesis to a significant degree[82].

Giving up smoking improves HDL levels, regardless of body weight, conducive to an improvement in cardiovascular health after smoking cessation[85].Cigarette smoking increases the oxidative modification of LDL. Exposure to cigarette smoke extract additionally diminishes the plasma activity of paraoxonase, an enzyme that protects against LDL oxidation[63]. There are 2 potential mechanisms by which reactive smoke components can produce their deleterious effects on essential plasma constituents: 1) indirectly, gas-phase cigarette smoke may activate macrophages and neutrophils in the lung (within the respiratory organ), which may release the enzymes and oxidants capable of damaging lipids and proteins; 2) directly, since the lung possesses an especially massive expanse area for gas exchange, it is possible that gas-phase cigarette smoke components interact with plasma constituents in the interstitial fluid[84].

Additional mechanisms are projected to clarify the link between smoking and changes in serum lipid and lipoprotein concentrations. Nicotine stimulates the discharge of adrenaline by the adrenal cortex (ductless gland), leading to augmented serum concentrations of free fatty acids (FFA) observed in smokers. As a result, lipolysis is increased along with the blood's triglyceride capacity. FFA are known to stimulate the hepatic secretion of VLDL and hence triglycerides. The increased release of FFA in the heart raises myocardial oxygen consumption, adding to the myocardial workload[86,87,88].The smoking-induced changes in serum lipid metabolism, the increased LDL/VLDL and attenuated HDL levels, together with the destruction of vascular endothelium, are associated with a bigger incidence of CAD (atherosclerosis) in smokers.

Increased risk of CAD among smokers is tobacco‘s effect on elevated overall blood cholesterol levels. This occurs as a result of the chemical substance acrolein, primarily used in pesticides, which affects the way the body processes cholesterol, permitting bigger amounts to remain in the blood system. This compound, among others, additionally decreases the ratio of HDL (the ―good cholesterol) to LDL (the ―bad cholesterol). LDLs and other fatty substances over time stick to the blood vessel walls and cause narrowing, a process known as atherosclerosis. These substances are called atheroma. If the atheroma ruptures and breaks off it leads to the formation of a thrombosis (clot). This sudden blockage of an artery may lead to a devastating heart attack, a stroke or gangrene of the leg[89, 90]. Thus, hypercholesterolemia and smoking are among the foremost vital factors that may lead to coronary artery disease[91, 92].

PROTHROMBOTIC STATE:

Cigarette smoking is well known to induce 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[93] and increased expression of tissue factor[94]. It induces alteration of fibrinolysis by inhibition of tissue plasminogen activator release from the endothelium and increase in plasminogen activator inhibitor-1 levels[95]. 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[96,97]. Smoking is associated with increased platelet-dependent thrombin generation[98]. 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. Carbon monoxide-induced relative hypoxemia leads to higher red cell mass, causing increase in blood viscosity, which also predisposes to thrombosis (Figure No.3)[99,100].

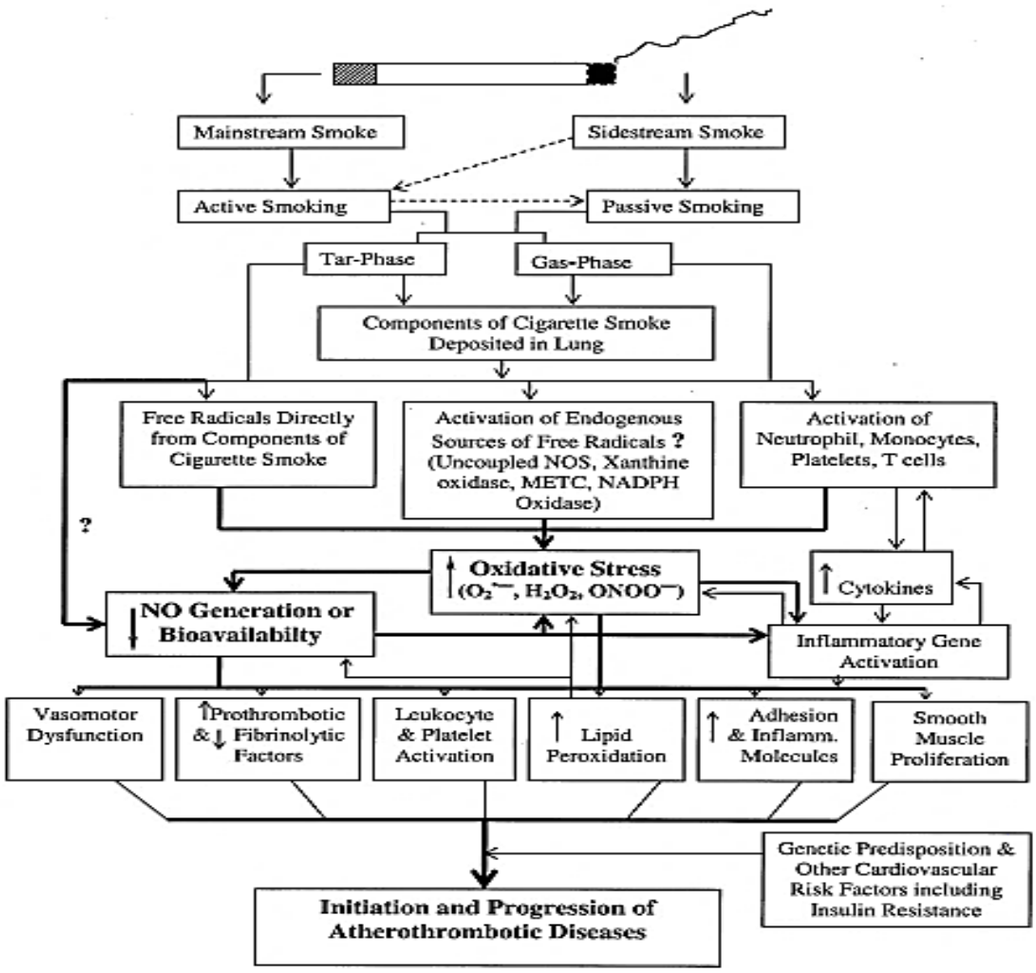

Figure No.3 Potential pathways and mechanisms for cigarette smoking-mediated cardiovascular dysfunction.

H_2O_2= hydrogen peroxide; METC=Mitochondrial electron transport chain; NADPH=Nicotinamide adenine dinucleotide phosphate reduced form; NOS=Nitric oxide synthase; ONOO= Peroxynitrite;
$O_2^{\cdot-}$ =Superoxide.

SMOKING AND INSULIN RESISTANCE:

Insulin has an effect on all the tissues of the body, either directly or indirectly and is characterized as a storage hormone owing to its anabolic action on all 3 chief dietary groups namely: carbohydrates, fats, and proteins. Insulin is associated with specific receptors within the cellular membrane. The fundamental functions of the insulin receptor are to spot and to bind the hormone with the target cell and to transmit its metabolic action. If one amongst these functions is disturbed, insulin resistance is manifested[101].

Nicotine is thought to extend sympathetic activity, to lift circulating levels of catecholamines, adrenocorticotropic hormone, prolactin, growth hormone, cortisol, and beta-endorphin, and to diminish estrogen levels[102] all these effects are powerfully antagonistic to insulin's action. Thus,

smoking reduces insulin productivity, slowing glucose catabolism and resulting in its accumulation within the body. Nicotine may additionally increase insulin resistance directly. It has been shown that the rise in insulin resistance was halted after nicotine replacement was stopped and even improved during continuous weight gain,[103] implying that nicotine rather than weight gain may be responsible for the initial increase in insulin resistance observed in some smoking-related studies[103,104].

The smoking-induced insulin resistance is also associated with an increase in triglyceride count[63] because in fatty tissue glucose is converted to triglycerides. In turn, owing to augmented serum concentrations of FFA and triglycerides, insulin-stimulated glucose transport in skeletal muscle of habitual cigarette smokers is relatively impaired in comparison with non-smokers[105]. Insulin resistance and the increase in triglycerides observed in smokers are significant risk factors for the long run development of arteriosclerosis and hence cardiovascular disease[106].

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[107]. 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[108]. Recently, it was shown that the CYBA gene A640G polymorphism might influence individual predispositions to CAD through interactions with smoking and hypercholesterolemia[109, 110].

SECONDHAND SMOKE EXPOSURE AND ITS LINK TO CARDIOVASCULAR DISEASE:

Exposure to second-hand 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 second-hand smoke each year in the United States[111], reflecting the increased risk in non-smokers of death due to CAD by approximately 20% in large epidemiologic studies[112]. The U.S. Surgeon General, in the 2006 report, estimated that living or working in a place where smoking is permitted increases the non-smoker's risk of developing CAD by 25–30% and lung cancer by 20–30%[113].

It has been shown that exposure to second-hand smoke in healthy young volunteer's 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 second-hand smoke increases CAD risk[114].There is no risk-free level of exposure to second-hand smoke[115]. Non-smokers who breathe second-hand smoke have a 25% –30 %

increases in the risk of developing a CVD[116].Each year, exposure to second-hand smoke kills 600,000 people: 28 percent of them are children. Of all adult deaths caused by second-hand smoke, more than 80 percent are from CVD[117]. In China and Bangladesh, more than half of all adults working indoors are exposed to second-hand smoke and in Russia, India and Ukraine it is more than one quarter[118].

THIRDHAND SMOKE:

The term ‘‘third-hand smoke’’ has been recently coined to identify the residual tobacco smoke contamination that remains after the cigarette is extinguished and second-hand smoke has cleared from the air[119,120]. It refers to the concept of contamination of surfaces by components of tobacco smoke. Among the substances in third-hand 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 third-hand smoke may pose a health risk, though the magnitude of risk and effect on cardiovascular system[121].

BENEFITS OF QUITTING SMOKING:

Smoking cessation almost completely eliminates the excess risk of CVD from past smoking. Physiological changes are evident within weeks after quitting, as well as a rapid resolution of the thrombotic state[122].In people who smoke 20 or a lot more cigarettes per day; the surplus risk of acute myocardial infarction is halved after about three to five years of quitting. The risk declines a lot slowly after that and a small residual risk still remains after 20 years[123]. Light smokers (<10 cigarettes per day) return to the risk level of the never smoker within about three years of quitting. Smokers who quit before the age of 35 years reverse all their excess risk of smoking-related disease[124]. In patients with pre-existing CVD, smoking cessation reduces total mortality by 36% compared with continuing to smoke[125]. This compares favorably with the risk reduction from other secondary preventative strategies such as use of statins (29%), ACE inhibitors (23%), β-blockers (23%) and aspirin (15%) [126]. Cessation also reduces the risk of stent or graft thrombosis and revascularisation[10].

Smoking cessation is additionally related to a considerable reduction in risk of stroke, peripheral arterial disease and erectile dysfunction. It has been speculated that post cessation weight gain could attenuate the cardiovascular benefits of quitting[127].Because of the extremely addictive nature of cigarette smoking; patients should not become discouraged if initial attempts to stop are unsuccessful. Repeated attempts are worth the effort, not only from the perspective of the individual smoker but also from that of their families and society at large, as well. The health consequences of continued cigarette smoking extend to healthy non-smokers through passive or second-hand smoking[128].Table No.1 lists some of the physical and psychological benefits of smoking cessation. It is important to note that even smokers who quit in their 60s experience not

solely an improved quality of life but an extended life expectancy compared with those who continue smoking[129].

Table No.1 Benefits of Smoking Cessation

SHORT-TERM BENEFITS	LONG-TERM BENEFITS
• Blood pressure returns to presmoking levels within 20 minutes. • Carbon monoxide levels drop within hours. • Money is saved each day by not buying cigarettes. • Sense of smell and taste improve within days. • Patient earns greater self-respect because of a real sense of accomplishment in quitting.	• Lung function improves up to 30% within 2 to 3 months. • Risk of coronary heart disease is reduced by 50% after 1 year. • Risk of stroke is similar to that of a non-smoker within 5 to 15 years. • Patient enjoys increased self-esteem due to quitting smoking.

CONCLUSION

Smoking cessation is an urgent priority for all smokers, particularly those with CVD. The cardiovascular risks from smoking are substantial but are largely reversible by quitting. Smoking is a substance use disorder and most smokers need help to quit. Smokers with CVD are likely to be more nicotine dependent and may need more intensive treatment and support.

Pharmacotherapy plays an important role in treating nicotine dependence. Based on the evidence so far, any cardiovascular risks from medication are likely to be small and are far outweighed by the advantages of quitting. Smoking is currently viewed as a chronic medical illness. The smoker needs to be re-engaged and assisted at regular intervals. The Healthcare professionals are well placed to assist smokers in quitting or at least refer them for further help when the opportunity arises. Altogether, smoking is the most important modifiable risk factor for cardiovascular disease, a major risk factor for cardiovascular morbidity and mortality, and is considered to be the leading preventable cause of death in the world.

Epidemiologic studies have established worldwide that cigarette smoke exposure is an important cause of cardiovascular morbidity and mortality. Clinical and experimental studies indicate that either active or passive exposure promotes vasomotor dysfunction, atherogenesis, and thrombosis in multiple vascular beds. Although the precise mechanisms responsible remain undetermined, free radical-mediated oxidative stress seems to play a central role in CS-mediated atherothrombotic diseases. These free radicals could potentially arise directly from cigarette smoke and indirectly from endogenous sources as well. Furthermore, potentiated by multiple prothrombotic and antifibrinolytic effects, intravascular thrombosis is the predominant cause of acute cardiovascular events.

An increasing body of epidemiologic, clinical, and experimental data also suggest that the pathophysiologic effects of cigarette smoke exposure on cardiovascular function may be nonlinear. Future studies investigating the potential cigarette smoke-inducible endogenous cellular mechanisms could further our understanding of the complex pathobiology of cigarette smoke and cardiovascular dysfunction. CVD's are a major health challenge. Smoking plays a major role in cardiovascular pathophysiology and efforts are required to address the problem especially at the preventive level. Different measures including public education and legislations have proved effective in different parts of the developed countries by reducing emergency admission in hospital. Legislated bans on smoking are associated with reduced rates of admission to hospital, reinforcing the value of such bans to public health. Consistent evidence also reports that exposure to second-hand smoke is detrimental to health.

This review adds to a growing body of proof that smoke-free legislation leads to reductions in the incidence of myocardial infarction. Developing countries ought to use this evidence-based body of data to make policies that will cut back the exaggerated trend of smoking among the population. The main target of anti-tobacco programs should not solely prevent young adults from starting smoking, but also promote quitting in current smokers. The latter are at high risk of developing a significant vascular event (or tobacco-related cancer) in the future. The adverse health effects of exposure can take a few years to look, whereas the advantages of withdrawal appear much more rapidly. Therefore, a strategy to facilitate quitting in current middle-aged smokers is probably going to possess a considerable health profit among a comparatively short time.

CONFLICT OF INTEREST:

The authors declare that there is no potential conflict of interests regarding the publication of this article.

ACKNOWLEDGEMENT:

Both the authors would like to thank Bharathi College of Pharmacy, Bharathinagara, Mandya, Karnataka, India for continuous support and encouragement throughout this work.

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