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A MINI-REVIEW ON NICOTINE AND ITS CARDIOVASCULAR EFFECTS

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Abstract

Nicotine is a naturally-occurring alkaloid found primarily in tobacco. It is most commonly absorbed from cigarette smoke. A cigarette contains 10 to 15mg nicotine and delivers on average 1mg nicotine to the smoker. Nicotine is also available from smokeless tobacco (snuff, chewing tobacco), pipe and cigar tobacco, waterpipe tobacco, and a variety of smoking cessation medications. Nicotine is also present in some insecticides, which may be a source of accidental or intentional poisoning. About 17% of nicotine is excreted unchanged in urine, with rate of urinary excretion is pH-dependent, decreasing in alkaline urine. Nicotine is found in milk of lactating women; with concentrations that parallel those of plasma. But, approximately 80 to 90% of nicotine is metabolized by lung, liver, and kidney; the principle metabolite is cotinine, which has a plasma concentration that is 10-fold higher than nicotine. In fact, nicotine itself even has some benefits. For instance, author linked chewing nicotine gum with improved short-term memory, and less likely to develop Parkinson's disease, reduce stress and anxiety, and stabilize mood. Nicotine is used as an insecticide since the 1690s, as tobacco extracts, but not commercially available in the US since 2014, and homemade pesticides are banned on organic crops and not for small gardeners. Nicotine pesticides have been banned in the EU since 2009. Foods are imported from countries in which nicotine pesticides are allowed, such as China, but foods may not exceed maximum nicotine levels. Neonicotinoids derived from and structurally similar to nicotine, are widely used as agricultural and veterinary pesticides as of 2016.

Key words: Nicotine, Cardiovascular effects, Mini-overview

Introduction

Nicotine is a naturally-occurring alkaloid found primarily in tobacco. It is most commonly absorbed from cigarette smoke. A cigarette contains 10 to 15mg nicotine and delivers on average 1mg nicotine to the smoker. Nicotine is also available from smokeless tobacco (snuff, chewing tobacco), pipe and cigar tobacco, water-pipe tobacco, and a variety of smoking cessation medications. It is also present in some insecticides as a source of accidental or intentional poisoning.

Pharmacokinetics: The peak plasma nicotine concentration during smoking is 10 to 50ng/mL with about 5 percent being protein bound. The half-life averages two hours. Approximately 80 to 90 percent of nicotine is metabolized by lung, liver, & kidney; the principal metabolite is cotinine, which has a plasma concentration that is 10-fold higher than nicotine. Cotinine has a half-life of 15 to 20hrs and is used a biomarker of 15 to 20hrs and is used a biomarker of nicotine exposure (Hukkanen *et al,* 2005).Nicotine is found in milk of lactating women with concentrations that parallel those of plasma.

Racial differences in tobacco-related diseases are not fully explained by cigarette-smoking behavior. Despite smoking fewer cigarettes per day, blacks have higher levels of serum cotinine. A study comparing the daily intake and rate of metabolism of nicotine in black and white smokers found that the tobacco smoke and nicotine intake per cigarette was 30% higher in blacks, while total and nonrenal clearances of cotinine were significantly lower (by 10 to 15%) in blacks. Thus, both a higher nicotine intake and slower rate of cotinine metabolism account for the higher serum cotinine concentrations in blacks (Pérez-Stable *et al,* 1998).

Genetic considerations: 1- CYP2A6 gene: Interindividual variability in plasma concentrate-ions of nicotine and cotinine is considerable during smoking, even among individuals taking in similar doses of nicotine. Nicotine is metabolized primarily by liver enzyme CYP2A6. A number of CYP2A6 gene variants were described; many of them are associated with slower metabolism of nico-

tine. Some individuals were described with CYP2A6 gene deletions who metabolize nicotine unusually slowly and generate little cotinine. Gene variants associated with slow metabolism are more prevalent among Asians and blacks. Genetically slow metabolizers tend to smoke fewer cigarettes per day and are able to quit smoking more easily than fast metabolizers (Malaiyandi *et al,* 2005).

2- Nicotinic receptor genes: Nicotine acts on nicotinic cholinergic receptors, which are comprised of five subunits. The receptors containing alpha 4 & beta 2 subunits mediate nicotine addiction. Alpha 3 beta 4 containing receptors mediate cardiovascular effects of nicotine. Specific cholinergic nicotinic receptor subunit (CHRN) genes, which encode nicotinic acetylcholine receptor subunits, that are associated with an increased risk for nicotine dependence and heaviness of smoking and with increased risk of smoking-related diseases such as lung cancer, peripheral vascular disease, and COPD were identified. Single nucleotide polymorphisms covering the complete family of 16 CHRN genes are assessed in nicotine-dependent cases and non-dependent controls (Stevens *et al,* 2008). A significant association between gene loci & nicotine dependence (2 distinct loci in CHRNA5-CHRNA3-CHRNB4 gene cluster, one locus in CHRNB3-CHRNA6 gene cluster, and a 4th in CHRND-CHRNG gene cluster) were described. Each appears to influence the transition from smoking to nicotine dependence (Saccone *et al,* 2009).

Drug interactions: Cigarette smoking interacts with a number of drugs. Most interactions are caused by the effects of combustion products (such as polycyclic aromatic hydrocarbons) that induce drug metabolism. Although some are mediated by actions of nicotine, the latter are primarily related to sympathetic nervous stimulation and catecholamine release. The following effects may occur with the cessation of smoking (Benowitz, 1996): 1- There is de-induction of hepatic enzymes which may require a reduction in dose of certain drugs include caffeine, clozaine, erlotinib, flecainide, fluvoxamine, imipramine, irinotecan, imipramine, olanzapine, pentazocine, propranolol, tacrine, and theophylline. 2-There is an increase in absorption of subcutaneous insulin which may require a decrease in dose.

Cardiovascular effects: Nicotine is a ganglionic and central nervous system stimulant, the actions of which are mediated via nicotinic cholinergic receptors. Nicotine binds to nicotinic cholinergic receptors that are located in the brain, autonomic ganglia, adrenal glands, and at neuromuscular junctions. These receptors that show diversity in subunit structure, function, and distribution within nervous system, presumably mediate complex actions of nicotine described in tobacco users (Benowitz *et al,* 1984). Major of nicotine cardiovascular effect is sympathetic neural stimulation (Cryer *et al,* 1976). Central nervous system-mediated sympathetic stimulation can occur through activation of peripheral chemoreceptors, a direct effect on the brainstem, and effects on caudal portions of spinal cord. The site appearing most sensitive to low levels of nicotine is the carotid chemoreceptor. Peripheral mechanisms includes catecholamine release from the adrenal and direct release or enhancement of release of catecholamines from vascular nerve endings (Narkiewicz *et al,* 1998).

Nicotine also enhances the release of various neurotransmitters, including epinephrine, norepinephrine, dopamine, acetylcholine, serotonin, vasopressin, glutamate, nitric oxide, calcitonin growth-related peptide, and betaendorphin. Some of these may contribute to the effects of nicotine on blood vessels (Okamura and Toda, 1994). Biphasic actions are observed depending upon the dose administered. The main effect of nicotine in small doses is stimulation of all autonomic ganglia; with larger doses, initial stimulation is followed by blockade of transmission. Biphasic effects are also evident in the adrenal medulla; discharge of catechola mines occurs with small doses, whereas prevention of catecholamines release is seen

with higher doses as a response to splanchnic nerve stimulation (Kannel, 1978).

Nicotine and cardiovascular risk: Smoking is an important and established risk for myocardial infarction and other coronary events, as angina pectoris (Wilhelmsen, 1988). The mechanisms by which cigarette smoking accelerates atherosclerosis and precipitates acute coronary events are complex. The main responsible constituents are combustion products, including oxidizing chemicals, acrolein, butadiene, metals (as cadmium), polycyclic aromatic hydrocarbons, particulates, and carbon monoxide. Oxidizing chemicals increase free radicals, increase lipid peroxidation, and contribute to several potential cardiovascular disease mechanisms, as inflammation, endothelial dysfunction, LDL oxidation & platelet activation (McBride, 1992).

Nicotine may also contribute to acute coronary events. There are a number of ways in which nicotine can affect the cardiovascular system to increase the risk of atherosclerosis and cardiovascular events such as myocardial infarction (Freestone and Ramsay, 1982).

Increased myocardial work: Smoking repeatedly produces a transient rise in BP of approximately 5 to 10 mmHg (Pickering *et al,* 1995). This effect is most prominent with the first cigarette of the day in habitual smokers. The hemodynamic effects of cigarette smoking are mediated by nicotine that increases heart rate up to 10 to 20 beats/ min after an individual cigarette and on average seven beats per minute throughout the day (Kool *et al,* 1993). Tobacco use is the most common cause of avoidable cardiovascular mortality world-wide. The immediate noxious effects of smoking are related to sympathetic nervous over-activity that increases myocardial oxygen consumption by a rise in blood pressure, heart rate, and myocardial contractility (Najem *et al*, 2006). Chronically, cigarette smoking induces arterial stiffness which may persist for a decade after smoking cessation (Jatoi *et al,* 2007). Hypertension incidence increased among those who smoke 15 or more cigarettes per day, and the coexistence of hypertension and smoking decreases left ventricular function in asymptomatic people (Bowman *et al,* 2007). With each cigarette, the blood pressure rises transiently and the pressor effect may be missed if the blood pressure is measured 30 minutes after the last smoke. Transient rise in blood pressure may be most prominent with the first cigarette of the day even in habitual smokers. In normotensive smokers, there was an average elevation in systolic pressure of 20mmHg after the first cigarette (Groppelli *et al,* 1992). Also, ambulatory blood pressure monitoring suggests an interactive effect between smoking and coffee drinking in patients with mild essential hypertension, resulting in a mean elevation in daytime systolic pressure of about 6.0 mmHg (Narkiewicz *et al,* 1995). The increased myocardial work, myocardial oxygen demands and coronary artery blood flow increase. But, myocardial ischemia may ensue in coronary patients, particularly in the presence of underlying coronary vascular disease when the coronary vasoconstrictive effect of smoking is superimposed.

Despite these acute effects, habitual smokers generally have **lower** blood pressures than nonsmokers (Mikkelsen *et al,* 1997). This is seen when blood pressure is measured after a period of nonsmoking, as is usually the case when a smoker is seen in the office or hospital. Ambulatory blood pressure recording shows that smoking increases blood pressure. The mild reduction in BP in smokers may be related to reduced blood volume that is seen as a consequence of nicotine mediated vasoconstriction and possibly decreased body weight, which reflects a nicotine-induced stimulation of energy expenditure (Perkins *et al,* 1989). A vasodilator effect of cotinine, the major metabolite of nicotine, also may contribute to the hypotensive response (Benowitz and Sharp, 1989).

Coronary vasoconstriction: In subjects with coronary disease, Doppler measurements of coronary blood flow demonstrate that cigarette smoking constricts epicardial

arteries, increases total coronary vascular resistance, and reduces coronary blood flow (Klein *et al,* 1984), and also reduces coronary vasodilatory flow reserve. Smoking has also been associated with an increased risk of vasospastic angina and poorer response of recurrent coronary spasm to vasodilator medication. Smoking can produce acute vasospasm during angiography (Quillen *et al,* 1993). These effects were mediated by increased catecholamines since the acute increase in coronary vascular resistance can be minimized by alpha-adrenergic blockers (Winniford *et al,* 1986).

Cerebral circulation: The effects of acute smoking and nicotine on the cerebral circulation are controversial. In an animal model, smoking a single cigarette produced a biphasic effect on cerebral arteriolar tone, resulting in both constriction and dilation; repeated smoking attenuated vasodilation (Iida *et al,* 1998). Vasodilatation is most likely an effect of nicotine, mediated, in part, by sympathetic activation, nitric oxide production, and potassium channel activation. Vasoconstriction is partially due to release of thromboxane A2 induced by cigarette smoke.

Hypercoagulable state: Cigarette smoking produces a hypercoagulable state, associated with platelet activation, increased red blood cell mass, and increased fibrinogen levels (Meade *et al,* 1987). Individuals who smoke have increased platelet aggregation, primary induced by oxidants in smoke and possibly also promoted by elevated catecholamine levels (Benowitz *et al,* 1993). Fibrinogen, identified in the Framingham study as a predictor of coronary events, is increased and, in association with elevated red blood cell mass (a consequence of carbon monoxide-mediated functional hypoxemia), will increase blood viscosity. Upon smoking cessation, plasma fibrinogen levels decrease; but, the full normalization may take several years (Kannel *et al,* 1987).

Thrombosis is a major factor in acute vascular events in smokers (Hung *et al,* 1995). Cigarette smoking increases the risk of acute myocardial infarction and sudden death much to a greater extent than it increases the risk of angina pectoris. Support for a role for thrombosis comes from studies showing that smokers who died with acute myocardial infarction were more likely to have thrombotic occlusion at autopsy, and smokers with AMI have more extensive thrombosis and less severe underlying CAD compared to non-smokers (Burke *et al,* 1997). While oxidant chemicals are thought to be most responsible for smoking-induced thrombosis, nicotine has been shown to increase the endothelial cell production of plasminogen activator inhibitor-1, which is a major regulator of fibrinolysis (Zidovetzki *et al,* 1999). Thrombolysis, defined as the dissolution of thrombus or, more specifically, breakdown of fibrin (fibrinolysis), is a critical component of vascular homeostasis. If not for an intact fibrinolytic system, even the smallest thrombus required to stem blood loss following minor vessel wall injury would progress rapidly and potentially compromise tissue per-fusing blood flow. Furthermore, intravascular fibrinolysis represents a vital teleologic defense mechanism, preventing "hemostasis in the wrong place" that could, under pathologic conditions, occur in the coronary arterial bed and cerebral vasculature (Kohler and Grant, 2000)

Further supporting the role of thrombosis are seen from several studies that smokers who receive a thrombolytic agent for an acute myocardial infarction have a better outcome than nonsmokers (Grines *et al,* 1995). In TIMI II trial, the mortality at 42 days was lower in current and ex-smokers compared to nonsmokers; 3.6 & 4.8 vs. 8.0%, $p<0.001$ (Mueller *et al,* 1992). The largest trial to evaluate the impact of cigarette smoking on outcome was GUSTO I which included 11,975 nonsmokers, 11,117 ex-smokers, and 17,507 current smokers. Non-smokers had significantly higher 30 day mortality than smokers (10.3 vs. 4.0%). The lower mortality in smokers could be explained by younger age and less severe underlying coronary ar-

tery disease, both consistent with thrombosis playing a major role in acute myocardial infarction (Barbash *et al,* 1995). Also, suppored hypothesis that thrombosis is a major mechanism of smoking-related coronary events is the observation that smokers who continue to smoke after thrombolysis or angioplasty have a substantially increased risk of reinfarction or reocclusion (Rivers *et al,* 1990).

Inflammation: Cigarette smoking results in a chronic inflammatory state, evidence increa-sed leukocyte count, C-reactive protein, and acute phase reactants such as fibrinogen. Smo-king also activates monocytes and enhances recruitment and adhesion of leukocytes to blood vessel walls, an integral step in vascular inflammation.

Lipid metabolism: Cigarette smoking has, via an unknown mechanism, an adverse effect on the lipid profile. In many patients hyperlipidemia is caused by some underlying "non-lipid" disease rather than a primary disorder of lipid metabolism. The secondary causes of dyslipidemia will be reviewed briefly here; many of these are discussed in more detail elsewhere: Type 2 diabetes mellitus cholestatic liver diseases nephrotic syndrome chronic renal failure hypothyroidism cigarette smoking obesity drugs (Holven *et al,* 2017). While the mechanisms of this effect are not fully understood, catecholamine-mediated increases in adipocyte lipolysis and increased re-esterification of free fatty acids by the liver are thought to contribute. Compared with nonsmokers, smokers have higher serum levels of triglycerides and lower levels of high density lipoprotein (HDL) cholesterol. In screening phase of beza-fibrate infarction prevention study group, e.g.; mean serum HDL-cholesterol level was 39.6mg/dL (1.03mmol/L) in nonsmokers, 37.2mg/dL (0.97 mmol/L) in former smokers, and 35mg/dl (0.91 mmol/L) in current smokers of two packs per day or more (Mjøs, 1988).

Smokers may also have higher levels of oxidized LDL believed to promote atherogenesis (Freeman *et al,* 1993). Lipids, such as cholesterol and triglycerides, are insoluble in plasma and circulating lipid is carried in lipoproteins that transport the lipid to various tissues for energy utilization, lipid deposition, steroid hormone production, and bile acid formation. The lipoprotein consists of esterified and unesterified cholesterol, triglycerides, and phospholipids, and protein. The protein components of the lipoprotein are known as apolipoproteins (apo) or apoproteins. The different apolipoproteins serve as cofactors for enzymes and ligands for receptors (Cochain *et al,* 2018).

The lipid changes induced by smoking are fully reversible within one to two months after smoking cessation (Terres *et al,* 1994). It remains unclear, however, whether these changes contribute to the increased risk of coronary disease. Data from the Lipid Research Clinics trial in which almost 7500 men and women in 10 North American populations were followed for an average of 8.5 years, the adverse effect of smoking on coronary disease appeared to be independent of LDL- and HDL-cholesterol (Criqui *et al,* 1987). Smoking and second hand smoke exposure also causes an increase in arterial lipid lesions (Sun *et al,* 2001).

Endothelial dysfunction: Cigarette smoking produces endothelial damage and impairs flow-mediated, endothelium-dependent peripheral arterial vasodilation, both in coronary and peripheral arteries, an effect that is partly reversible after smoking cessation (Neunteufl *et al,* 2002). In contrast, endothelium-independent vasodilation is preserved (Campisi *et al,* 1988). The endothelium has been considered an inert barrier to elements contained in the blood. However, evidence indicates that the endothelium is an active biologic interface between the blood and all other tissues. The single layer of continuous endothelium lining arteries and veins forms a unique thromboresistant layer between blood and potentially thrombogenic subendothelial tissues. Endothelium also modulates tone, growth, hemostasis, and inflammation throughout the circulatory system.

Importantly, an excessive inflammatory and fibroproliferative response to the number of insults to the vascular endothelium is important in the development of atherosclerosis (Konukoglu and Uzun, 2017). Oxidizing chemicals and nicotine appear to be responsible for endothelial dysfunction.

Smokers, particularly those with coronary atherosclerosis, have a paradoxical response to acetylcholine in which vasoconstriction rather than normal vasodilation is seen. This abnormality appears to result from impaired release of endothelium-derived relaxing factor, nitric oxide (Kiowski *et al,* 1994).

Nitric oxide release has potential beneficial cardiovascular effects include vasodilation & reductions in platelet aggregation, smooth muscle cell proliferation, and adhesion of monocytes to endothelium. Cigarette smoking impairs release of nitric oxide, which could contribute to both acute cardiovascular events and accelerated atherogenesis.

Carotid artery intimal-medial thickness & cigarette smoking: Atherosclerosis Risk in Communities Study (ARIC) evaluated the association between carotid artery wall thickness and active and passive cigarette smoking in 12,953 men and women, aged 45 to 65 years (Howard *et al,* 1994). Increased carotid intimal-media thickness (C-IMT) was noted with a progressive increase in frequency in each of the following groups: never smokers reporting no exposure to environmental tobacco smoke (ETS), never smokers reporting weekly exposure to ETS or "passive smoking" of at least one hour, past smokers, and current smokers. Similar data were noted among 1800 patients at a lipid clinic (Baldassarre *et al,* 2009).

Smokeless tobacco: Various forms of smokeless tobacco, such as oral snuff or chewing tobacco, are used widely (WHO, 2006). An estimated 8.1 million (3.2%) people in the US use smokeless tobacco products (Christen *et al,* 1982). Among adults older than 18 years in the United States, smokeless tobacco product use is more prevalent in men than women, and overall, individuals between 18 and 25 years of age are most likely to be users of smokeless tobacco products. In the United States, chewing tobacco prevalence (loose leaf, plug, & twist) use declined since mid-1980s (WHO, 2008).

Nicotine is the principal alkaloid found in smokeless tobacco products. The amount of total and free nicotine varies substantially. The concentrations of nicotine (milligrams per gram of tobacco) are similar in oral snuff and cigarette tobacco and somewhat lower in chewing tobacco (Djordjevic and Doran, 2009). Most smokeless tobacco products are held in the mouth, cheek, or lip or chewed to allow absorption of nicotine across the buccal mucosa. Oral snuff is held in the cheek between the gum and tooth area (Hatsukam *et al,* 2007)

The cardiovascular risks of smokeless tobacco were evaluated, with the following being the important findings.

Hypertension: Data from the majority of smokeless tobacco studies do not support an increase in the incidence or prevalence of hypertension (Hergens *et al,* 2005). One exception is that snuff is associated with a small but significant increase in the relative risk for hypertension. In a longitudinal study of Swedish construction workers, followed between 1978 & 1993, almost 30% of men used snuff. Adjusted odds ratio of high blood pressure amongst snuff users at baseline was 1.23 (95% CI 1.15-1.33) compared to never snuff users. Relative risk of high blood pressure during follow-up was 1.39 (95% CI 1.08-1.79) amongst snuff users (Hergens *et al,* 2008)

Proposed mechanisms by which smokeless tobacco might increase blood pressure are as follows. Some smokeless tobacco products, such as loose snuff and chewing tobacco, contain large amounts of sodium, part of the sodium bicarbonate alkaline buffer, enhancing nicotine absorption. Sodium load (30 to 40 excess mEq/day) could potentially aggravate hypertension and heart failure (Benowitz, 1988a). Some smokeless tobacco products contain significant amounts

of licorice. Glycyrrhizinic acid, an active chemical in licorice, has mineralocorticoid activity, which potentiate hypertension and potassium wasting (Benowitz *et al,* 1988).

Among "one-time" users of snuff or chewing tobacco transient (30 to 60 minutes), increases in blood pressure and heart rate have been observed due to effects of nicotine. Moreover, in data from studies in subjects with a history of tobacco use, the acute effects of smokeless tobacco products include an increase in heart rate and no change or transient increases in blood pressure. A crossover study examined circadian blood pressure and heart rate after four types of nicotine use: smoking cigarettes, oral snuff, chewing tobacco and no tobacco use. Three of these, that is, smoking cigarettes, oral snuff, and chewing tobacco were associated with a significant increase in heart rate throughout the day but no change in blood pressure (Benowitz, 1988b).

Mortality and myocardial infarction: Population-based studies have evaluated the risk for nonfatal and fatal coronary heart disease events in smokeless tobacco users (Piano *et al,* 2010). Three studies have been conducted in the United States. The first National Health and Nutrition Examination Survey (NHANES) Epidemiological follow-up study did not find association between smokeless tobacco products and either all-cause or cardiovascular mortality (Accortt *et al,* 2002). But, in two other US studies, Cancer Prevention Study I (CPS-I) and CPS-II, current smokeless tobacco use was associated with an increased hazard ratio for all-cause mortality as well as mortality related to coronary and cerebrovascular disease (Henley *et al,* 2005). Some have minimized findings related to CPS-I because the data were collected between 1959 & 1972 when there was a greater prevalence of cardio-vascular disease (Critchley and Unal, 2004).

The overall risk of cardiovascular disease (CVD) in smokeless tobacco users was estimated in two meta-analyses that include reports from both Sweden and the US (Lee, 2007). One report found that smokeless tobacco use was not associated with a significantly increased risk of heart disease (RR 1.12, 95% CI: 0.99 to 1.27). In the other, ever-use of smokeless tobacco products was associated with an increased risk of fatal myocardial infarction (RR of 1.13, 95% CI: 1.06 to 1.21) and fatal stroke (RR or 1.4, 95% CI: 1.28 to 1.54). The increased risk was attributed to the inclusion of the US studies, which found an increased hazard ratio for all-cause coronary and cerebrovascular disease (Boffetta and Straif, 2009).

Data derived from the inter-heart study, a 52 country international study, reported on outcomes from a variety of tobacco products. Data from inter-heart showed that chewing tobacco alone was associated with significantly increased myocardial infarction risk. Subjects who chewed tobacco had a significantly increased risk of a myocardial infarction (odds ratio [OR] 2.23; 95% CI: 1.41 to 3.52) compared with those who never used tobacco (Teo *et al,* 2006) and also, smokers who chewed tobacco had the highest risk for acute myocardial infarction.

Mechanism of action of second hand smoke: Second hand smoke exposure is associated with an increased risk of acute coronary events, including acute myocardial infarction. The effects of second hand smoke exposure on the number and function of endothelial progenitor cells, plasma vascular endothelial growth factor, circulating endothelial microparticles, and flow-mediated vasodilation were evaluated for 24hrs after brief exposure of real-world levels of smoke to 10 normal volunteers. Brief exposure not only causes acute vascular injury as indicated by endothelial dysfunction and microparticle generation, but also leads to sustained changes of the vascular repair system with a mobilization of dysfunctional endothelial progenitor cells. Mechanistically, these effects are linked to an impairment of or no production in endothelial progenitor cells. Taken together, these findings provide evidence that even a very short period of pas-

sive smoke exposure has strong, persistent vascular consequences (Institute of Medicine, 2010).

Second hand smoke may harm the vasculature not only by directly injuring the vascular endothelium, but also by interfering with the vascular repair system, which may lead to chronic damage with recurrent exposures. These results indicate that involuntary second hand smoke exposure constitutes a risk even at low levels (Heiss *et al,* 2008).

Insulin resistance: Cigarette smoking increases the risk of type 2diabetes and insulin resistance. Patients with insulin resistance have an increased risk of coronary disease (Willi *et al,* 2007). The metabolic syndrome-otherwise called syndrome X, insulin resistance syndrome, Reaven syndrome, and "the deadly quartet"-is the name given to the aggregate of clinical conditions comprising central and abdominal obesity, systemic hypertension, insulin resistance (or type 2 diabetes mellitus), and atherogenic dyslipidemia. It is a prothrombotic and proinflammatory state characterized by increased inflammatory cytokine activity. Besides, inflammatory dermatoses such as psoriasis, lichen planus, and hidradenitis suppurativa, metabolic syndrome is also commonly associated with accelerated atherosclerotic cardiovascular disease, hyperuricemia/gout, chronic kidney disease, and obstructive sleep apnea. Current therapeutic options for metabolic syndrome are limited to individual treatments for hypertension, hyperglycemia, and hypertriglyceridemia, as well as dietary control measures and regular exercise. (McCracken *et al,* 2018). Nicotine, most likely mediated via catecholamine release, contributes to the development of insulin resistance. This was illustrated in one study of 40 non-obese middle-aged men, which found that the long term use of nicotine-containing chewing gum was associated with the presence of insulin resistance and hyperinsulinemia. There was a correlation between the extent of nicotine use and the degree of insulin resistance (Eliasson *et al,* 1996).

Safety of nicotine replacement therapy: Risks associated with nicotine replacement therapy in patients with cardiac disease have been of concern. Smokers and ex-smokers are at increased risk for acute myocardial infarction and other coronary events; however, establishing a causal relation between nicotine replacement and cardiovascular events is problematic since acute cardiovascular events are common in smokers and cardiac risk persists beyond the time of smoking cessation.

Nicotine replacement delivered by nicotine polacrilex gum (Nicorette), nicotine lozenges, nicotine nasal spray, and transdermal nicotine (Habitrol, Nicotrol, Nicoderm) has effects comparable to cigarette smoking with respect to increasing myocardial work. However, the risk of smoking while using nicotine replacement therapy appears no greater than the risk of smoking alone. The apparent absence of added risk may reflect both the relatively flat dose-response relation for nicotine and the fact that, even with continued smoking during nicotine replacement, total intake is modest compared with usual smoking because the amount of cigarettes smoked is usually less during nicotine replacement (Benowitz and Gourlay, 1997)

Lung Health Study cohort of 5887 middle-aged smokers with chronic obstructive pulmonary disease who were followed for five years compared smokers to those who quit with or without nicotine gum. There was no increase in hospital admission for cardiovascular events with nicotine gum treatment, regardless of the dose used. Participants who quit smoking and used nicotine gum had a lower hospital admission rate for cardiovascular disease than subjects who did not quit smoking, regardless of whether or not they used the gum (Murray *et al,* 1996).

The results of two other controlled trials of nicotine replacement and one population based case-control study in patients with cardiovascular disease also provided no evidence for an increase in coronary events with replacement therapy. As an example, a

randomized trial of 584 patients (almost all men) with at least one diagnosis of cardiovascular disease found no difference in the incidence of primary cardiovascular end points (death, myocardial infarction, cardiac arrest, and admitted to hospital for cardiovascular disease) at 14 weeks between nicotine and placebo groups (5.4 vs. 7.9% with placebo). Evidence suggested that chemicals other than nicotine elevated risks of myocardial infarction and stroke in smokers. Risks of nicotine medication in cardiovascular patients, if any, are much lower than those of smoking, and benefits of nicotine medication far outweigh risks of continued smoking in such patients (Joseph *et al,* 1996).

Smoking cessation: Smoking cessation reduces cardiovascular morbidity and mortality for smokers with or without cardiovascular disease, but is particularly important for patients at high risk for coronary events. Smoking cessation is often difficult for cardiovascular patients. Most are highly addicted as evidenced by the fact that they are still smoking despite advice that smoking is extremely hazardous to their health, and smoking cessation is difficult for such patients. Several characteristics have been identified that distinguish patients who find it difficult to quit smoking after a cardiac event. These include: a- Lower occupational and educational level, b- Increasing age, c- Higher rates of alcohol consumption or drug abuse, d- History of depression and other psychiatric diseases, and e- A low sense of personal control over activities of daily life (Kimmel *et al,* 2001). Despite an understanding of risk, particularly among individuals at risk for recurrent coronary events, there is a high rate of failure in smoking cessation attempts. A number of approaches were tried in cardiovascular disease patients, including nicotine replacement, usually with gum or a patch, bupropion, and varenicline. Nicotine replacement therapy is widely used in critically ill smokers and its effect on delirium, mortality and duration of intensive care unit (ICU) admission is unknown. This review was to determine whether management of nictine withdrawal with nicotine replacement therapy reduces delirium, mortality or stay length in critically ill smokers in ICU. The primary outcome was incidence of author-defined ICU delirium. Secondary outcomes were ICU or hospital mortality, ICU-free days at day 28, & ICU or hospital stay length. In the meta-analysis studies, nicotine replacement therapy was associated with increased delirium (Ng *et al,* 2017)

Conclusion

Major cardiovascular effect of nicotine is sympathetic neural stimulation. Nicotine enhances release of various neurotransmitters, including epinephrine, norepinephrine, dopamine, acetylcholine, serotonin, vasopressin, glutamate, nitric oxide, calcitonin growth-related peptide, and beta-endorphin. Nicotine increased risk of cardiovascular events seen with cigarette smoking by transiently increasing blood pressure, causing coronary artery vasoconstriction and/or impairing endothelial function. Smokeless tobacco contains and delivers levels of nicotine similar to those of smokers, and may be associated with an increased risk of myocardial infarctionand/or stroke, although the risk is less than from cigarette smoking.

Risks associated with nicotine replacement therapy in patients with cardiac disease appear to be low and in any case are much less than the continued smoking risks. The benefits of nicotine medication to promote smoking abstinence or cessation far outweigh risks in cardiovascular disease patients.

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