Cardiovascular Remodeling Induced by Passive Smoking

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Abstract: Coronary heart disease (CHD) is the most common cause of death in many developed countries. The major risk factors for CHD are smoking, high blood pressure, diabetes, high cholesterol levels, and lack of physical activity. Importantly, passive smoke also increases the risk for CHD. The mechanisms involved in the effects of passive smoke in CHD are complex and include endothelial dysfunction, lipoprotein modification, increased inflammation and platelet activation. Recently, several studies have shown that exposure to tobacco smoke can result in cardiac remodeling and compromised cardiac function. Potential mechanisms for these alterations are neurohumoral activation, oxidative stress, and MAPK activation. Although the vascular effects of cigarette smoke exposure are well known, the effects of tobacco smoking on the heart have received less attention. Therefore, this review will focus on the recent findings as to the effects of passive smoking in acute and chronic phases of vascular and cardiac remodeling.

INTRODUCTION

Coronary heart disease (CHD) is the most common cause of death in many developed countries. The major risk factors for CHD are smoking, high blood pressure, diabetes, high cholesterol levels, and lack of physical activity [1,2]. Furthermore, smoking is a major risk factor for cancer and other atherosclerotic diseases such as stroke and peripheral vascular disease. Active smoking increases the risk of death from CHD at least two-fold and the risk of stroke by around 50% [3,4]. In the United States nearly 440,000 deaths occur annually due to smoking [5].

Epidemiological evidence has unequivocally confirmed that active smoking remains the leading cause of preventable death [6]. Interestingly, tobacco use is different from other lifestyle behaviors because it impacts not only the smoker but also those in proximity, namely, the passive or secondhand smokers. Almost 20 years ago, evidence of the harmful effects of passive smoke began to emerge [7,8]. Nowadays, passive smoke accounts for approximately 50,000 deaths per year in the United States [9].

The first report that showed increased CHD in passive smokers was published by the California Environmental Protection Agency in 1999 [10]. Since then, other reports have suggested a non-linear dose-response relationship between the intensity of exposure to tobacco smoke and the risk of ischemic heart disease [11,12]. Although active smokers are exposed to a total smoke dose 100 to 300 times higher than are passive smokers, the relative CHD risk for smokers is 1.78 compared with 1.31 for passive smokers [13]. Evidence of higher toxin concentration in sidestream smoke than that in its mainstream counterpart, and the interactions of mechanisms triggered by these substances may indicate increased CHD risk [14].

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The risks of passive smoking are not limited to CHD. Passive smoke causes lung, breast, head and neck cancers, chronic obstructive pulmonary disease and respiratory infections [15].

Due to the burden and costs of chronic diseases related to tobacco exposure, the WHO Framework Convention on Tobacco Control proposed in 2003 a set of policies to reduce demand for tobacco, such as increased taxes on tobacco products, enforcement of smoke-free workplaces, and public campaigns about the health risks of smoking [16]. These policies to reduce smoking prevalence combined with the increasing knowledge of the effects of passive smoking on the cardiovascular system may help to decrease the burden of environmental tobacco exposure. Importantly, the Centers for Disease Control and Prevention found that nearly one half of US nonsmokers continue to be exposed to passive smoke [17].

In addition to well known effects of smoking in the vascular system, several recent studies have shown that exposure to tobacco smoke can result in cardiac remodeling and compromised cardiac function. However, although the vascular effects of cigarette smoke exposure are well known, the effects of tobacco smoking on the heart have received less attention. Therefore, this review will focus on recent findings on the effects of passive smoking in the acute and chronic phases of vascular and cardiac remodeling.

PASSIVE SMOKE CHARACTERIZATION

The major source, by far, for passive smoke is sidestream smoke which is emitted from the burning end of a cigarette between puffs. The remainder of passive smoke consists of exhaled mainstream smoke, smoke that escapes from the burning end during puff-drawing, and gases that diffuse during smoking through the cigarette paper [18]. Also, the smoke has two different phases, a vapor and a particle phase. The hydrophilic vapor phase constituents are absorbed in the upper respiratory tract. Particles smaller than 2.5 μm can be inhaled deeply into the lungs, and are supposed to be more dangerous than the larger ones [18, 19].

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More than 4,720 compounds have been identified in cigarette smoke. The chemical constituents of sidestream smoke are distinct from those of directly inhaled smoke. Evidence supports the presence of higher concentrations of toxins (ammonia, volatile amines and nitrosamines, nicotine decomposition products and aromatic amines) and smaller particles in sidestream smoke [18, 20].

There is no current direct measure of the dose absorbed from environmental tobacco exposure. However, biological markers such as nicotine and its metabolite cotinine have great importance in assessing recent exposure to tobacco. Indeed, Whincup *et al.*, in a prospective study, highlighted the importance of using objective measures of tobacco exposure, such as cotinine [21].

Given the cardiovascular effects of tobacco smoke, passive smoke may induce vascular and cardiac remodeling, thus leading to increased risk for CHD death. The most important alterations will be discussed in detail below.

VASCULAR REMODELING

The vascular wall is an intricate active integrated organ composed of endothelial, smooth-muscle, and fibroblast cells. Vascular remodeling is an active process of structural alteration that involves cell growth, cell death, cell migration, and turnover of extracellular matrix. Vascular remodeling is usually an adaptive process that occurs in response to long-term changes in hemodynamic conditions, but it may subsequently contribute to the development of vascular diseases [22]. The pathophysiology of vascular remodeling is complex, but involves mainly endothelial dysfunction, lipoprotein alterations, inflammation, and platelet activation.

The endothelium plays a key role in vascular homeostasis and in regulation of vascular tone. For example, in response to increased blood flow and acetylcholine, the enzyme nitric oxide synthase uses L-arginine to generate nitric oxide (NO) in the endothelium, thus provoking vasodilation. On the other hand, in response to epinephrine, the endothelium secretes endothelin, leading to vasoconstriction. It is currently accepted that endothelial dysfunction predicts the initiation and progression of atherosclerosis [23]. Importantly, active and passive smoking can result in impaired endothelial function. In addition, impaired endothelium-dependent vasorelaxation is considered to be the earliest sign of endothelial dysfunction in smokers [24].

Given the vascular tone alterations induced by smoking, in the acute phase, passive smoke leads to an impairment of acetylcholine-induced coronary artery dilation, as well as to reductions of NO synthase activity and of arginine content in vascular endothelium [25-28]. Additionally, after 30 minutes of exposure to environmental smoke, there was significant reduction in coronary flow velocity reserve in nonsmokers, to the same degree as seen in active smokers [29]. Thus, exposure to a low dose of toxins may be sufficient to interfere with endothelial function. A different clinical study suggests that alterations in vascular tone induced by passive smoke were mediated through the nicotine-dependent pathway. Interestingly, impairment in microvascular function persists even after the end of the exposure [30]. Likewise, in the chronic phase, passive smoke also leads to endothelium-dependent vasodilation. For instance, Celermajer *et al.* found impaired arterial flow-mediated dilation after 3 years of tobacco exposure [31].

Besides alterations in vascular tone, passive smoke may also increase arterial stiffness, as reported after acute and chronic exposure to passive smoke, similar to the effects observed in active smokers [32-35]. Passive smoke may also cause direct damage to the endothelium by different pathways. Firstly, some studies suggest that oxidative stress may contribute to this damage [36,37]. Indeed, cigarette smoke increases production of superoxide anions, due to stimulation of NADPH, resulting in reduced NO levels and endothelial dysfunction [37]. In addition, endothelial cells exposed to tobacco showed morphological alterations, such as disruption of junctional complexes, abnormal cytoplasm vacuoles, compromised microtubules and augmented expression of surface cell adhesion molecules [38]. These molecules promote migration of monocytes into the vessel wall and their transformation into lipid-laden macrophages. In an animal model, there was leukocyte-endothelial adhesion after a 5-min exposure to one stream of cigarette smoke [39]. Finally, the endothelial cytoskeleton, in special actin filaments and circulating endothelial progenitor cells, is essential for repairing endothelial cell damage [40,41]. Passive smoke also disrupts the organization of actin filaments and is inversely correlated with the number and functional activity of endothelial progenitor cells [42,43]. Therefore, tobacco smoke is associated with direct endothelial damage and with disruption of the endothelial repair system.

In addition to endothelial alterations, passive smoke accelerates development and progression of atherosclerotic plaque due to lipoprotein pattern modification and inflammation.

Increased oxidative stress due to passive smoke converts low-density lipoprotein (LDL) to oxidized LDL, leading to formation of foam cells [44]. Even a short exposure to tobacco may lead to increased lipid accumulation in the artery wall [45]. Moreover, acute and chronic exposure to environmental smoke leads to lower levels of high-density lipoprotein (HDL) [46-48]. Although oxidative stress is a key factor in lipoprotein profile alteration, the mechanism by which smoke exposure affects lipid levels is not fully understood [5]. As a result, this new lipoprotein profile ($\downarrow$ HDL and $\uparrow$ LDL) leads to increased risk of atherosclerosis and of cardiovascular death.

Inflammation is also linked to atherosclerotic plaque development. Elevations of circulating markers in passive smokers – including C-reactive protein, homocysteine, fibrinogen, activated neutrophils and leukocyte count – reinforce the importance of inflammation in CHD induced by tobacco exposure [5,8,13]. Furthermore, increased levels of fibrinogen and homocysteine are associated with a pro-thrombotic state [49]. A recent study showed increased levels of tissue (aortic arterial wall) interleukin-8, monocyte chemoattractant protein-1, and vascular cell adhesion molecule-1 [50]. In addition, one hour of secondhand smoke exposure at bar/restaurant levels was accompanied by marked increases in inflammatory markers such as the cytokines IL-4, IL-5 and IL-6, as well as tumor necrosis factor (TNF)-α, and IFN-γ, particularly in men [51].

Thus, increased serum and tissue levels of these acute phase response proteins, associated with dysfunctional lipid metabolism contribute to effects of passive smoke on the cardiovascular system.

Platelet activation, another important effect of passive smoke, increases the risk of thrombus formation at sites of plaque disruption and plays a major role in acute coronary syndromes [52]. Non-smokers, after 20 minutes of exposure to passive smoke, displayed the same level of platelet activation as smokers [53]. Another study showed that sidestream smoke was about 1.5 times more potent than its mainstream counterpart in activating platelets [54]. Markers of platelet activation such as thromboxane and platelet α-granule constituents are also increased in passive smokers [55,56]. Thus, platelet activation, surprisingly, is more pronounced in passive than in active smokers. All these acute effects of passive smoke are probably transient and disappear after cessation of the exposure [30,57].

Therefore, vascular remodeling and platelet activation are major mechanisms of increased CHD in passive smokers. However, the effects of tobacco exposure on cardiac remodeling should not be ignored and will be discussed next.

CARDIAC REMODELING

Although the vascular effects of cigarette smoke exposure are universally accepted, the effects of tobacco smoking on the heart have received less attention.

Cardiac or ventricular remodeling is defined as alterations in size, geometry, shape, composition, and function of the heart after cardiac injury. Initially, ventricular remodeling may be a compensatory process, since the morphological adaptations are critical in preserving cardiac function in response to various injuries. However, chronic ventricular remodeling is now recognized as an important pathological process that results in progressive ventricular dysfunction and clinical presentation of heart failure or death [58-60]. Recent experimental and clinical studies evaluated the consequences of exposure to tobacco smoke as expressed by both functional and morphological cardiac variables.

The cardiac effects of the acute administration of nicotine or exposure to tobacco smoke were investigated in different experimental models. In an experimental study utilizing dogs, the acute administration of nicotine was accompanied by an increase in cardiac contractility [61]. Likewise, Houdi *et al.* exposed rats to cigarette smoke for 4 days and observed an increase in blood pressure and decrease in cardiac output. These effects were attenuated by a vasopressin antagonist [62]. Therefore, acute exposure to tobacco smoke appears to interfere with cardiac inotropism.

The chronic effects of smoke on cardiac remodeling have also been investigated. Usually, experimental rats are exposed to cigarette smoke in a modified incubator according to the method proposed by Simani *et al*., and Wang *et al*. [63,64]. Briefly, rats are exposed to cigarette smoke in a chamber connected to a smoking device. The smoke is drawn out of filtered commercial cigarettes with a vacuum pump and puffs of cigarette smoke are projected into the smoking chamber.

Different authors have shown that exposure to cigarette smoke is associated with morphological and functional cardiac alterations. Indeed, tobacco smoke induces enlargements of the left atrium and left ventricular chamber, myocardial hypertrophy, as well as reductions in left ventricular ejection indices such as systolic shortening fraction, fractional area change and ejection fraction [65-70].

The effects of cigarette smoke exposure in rats submitted to myocardial infarction were also analyzed. Cigarette tobacco exposure, before and after experimental myocardial infarction, intensified the cardiac remodeling process subsequent to coronary occlusion [71,72].

Therefore, the experimental data have consistently shown that chronic exposure to tobacco smoke is associated with cardiac remodeling and compromised ventricular function. Potential mechanisms for these alterations will be discussed below.

In a previous study, echocardiography revealed systolic dysfunction in rats exposed to cigarette smoke for one month. However, evaluation of the papillary muscle revealed no difference in cardiac function between rats exposed to tobacco smoke and controls. Similar results using isolated papillary muscle were reported by Brooks *et al*. [73]. The papillary muscle method allows evaluation of cardiac function without interference from heart rate, preload and afterload. Thus, intrinsic muscle properties are probably not involved in cardiac remodeling induced by smoke exposure, at least after the one-month follow-up.

Given the potential mechanisms involved in the hemodynamic changes induced by exposure to tobacco exposure, some studies provide strong evidence that such exposure results in elevated values of neurohormonal factors such as endothelin-1 and vasopressin, and increased blood pressure [74,75]. On the other hand, prior studies with longer observation periods (4 and 6 months) have not shown alterations in PO2 or in the percentage of hemoglobin O_2 saturation [66,67]. Thus, chronic hypoxemia and changes in blood viscosity secondary to hypoxia did not participate in the pathophysiology of the smoking-induced changes. Therefore, these data support the notion that hemodynamic alterations, mediated by neurohormonal activaction, participate in the smoking-induced cardiovascular actions.

It is well established that reactive oxygen species and oxidative stress play a critical role in the cardiac remodeling following different cardiac injuries [76,77]. Indeed, oxidative stress interferes with extracellular matrix, myocyte contractile proteins and myocyte hypertrophy, and can lead to myocyte death due to necrosis or apoptosis. To evaluate the role of oxidative stress in tobacco-induced cardiac remodeling, smoking rats were supplemented with beta-carotene. Animals exposed to tobacco smoke presented ultra-structural changes in electron microscopy such as disorganization or absence of myofilaments, infolding of plasma membrane, dilatation of sarcoplasmatic reticulum, as well as polymorphic and swelling mitochondria associated with decreased cristae. Importantly, the alterations were attenuated with beta-carotene supplementation [68]. Thus, the available data corroborate the participation of oxidative stress in the remodeling process induced by smoking.

Furthermore, some metalloproteinases (MMP), specifically MMP-2 and MMP-9, also called gelatinases A and B, have been related to cardiac remodeling. However,

there were no differences in MMP-2 or -9 activation between rats exposed to tobacco smoke for 4 months and controls [69]. Importantly, the participation of other MMPs in tobacco-induced cardiac remodeling was not evaluated.

Recently, Gu *et al*. showed that cigarette smoke-induced left ventricular remodeling is associated with activation of mitogen-activated protein kinases (MAPK) such as extracellular signal-regulated kinase (ERK1/2), p38-kinase (p38) and c-Jun NH2-terminal protein kinase (JNK) [70], findings that suggest a potential involvement of MAPK activation in cigarette smoke-induced left ventricular remodeling.

Finally, clinical studies have also analyzed the cardiac effects of smoking. Indeed, acute inhalation of cigarette smoke was accompanied by disorders in diastolic function [78]. In addition, in the MESA trial the results from magnetic resonance imaging demonstrated regional myocardial dysfunction in smokers, compared with nonsmokers, despite the absence of clinical manifestation of disease [79]. In the observational CARDIA study, smokers had a greater left ventricular mass when compared with nonsmokers assessed by echocardiogram [80], suggesting that smoking may induce cardiac alterations in humans.

CONCLUSION

Evidence of the harmful effects of passive smoke began to emerge 20 years ago. Since then, smoking regulation policies have decreased exposure to passive smoke. Despite that, the Centers for Disease Control and Prevention found that nearly one half of US nonsmokers continue to be exposed to passive smoke. Passive smoke increases the risk for CHD, chronic obstructive pulmonary disease, respiratory infections as well as lung, breast and neck cancers. The effects of passive smoke in CHD comprise endothelial dysfunction, lipoprotein modification, increased inflammation and platelet activation. Recently, cardiac remodeling induced by tobacco exposure was also demonstrated. Potential mechanisms for these alterations include neurohumoral activation, oxidative stress and MAPK activation, but not MMP activation. Policies to reduce smoking prevalence combined with the increasing knowledge of the effects of passive smoking on the cardiovascular system may help to decrease the burden of environmental tobacco exposure.

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