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Smoking and hypertension

Abstract

Smoking and hypertension are two well-known independent risk factors for both heart and blood vessel. A large number of observations identify cigarette smoke as a factor able to cause a functional and initially transient damage primarily of the endothelium and reduced tolerance to exercise stress testing because of the effects of nicotine and carbon monoxide. At the time, the functional damage became an irreversible pathological damage with ischemic lesions of the myocardium and artery vessel atherosclerosis. In its turn, hypertension plays harmful effects on the heart, kidney and arterial tree, mainly coronary, carotid and cerebral vascular structures, by its complications, the target organs of which are the same of cigarette smoke. There is evidence that the association of cigarette smoking with hypertension exponentially increases the risk of cardiovascular disease and events when compared to that of each of these factors singly acting.

Keywords: smoking, hypertension, combined action, heart damage, artery vessel damage

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Introduction

Cardiovascular risk factors play a significant role to influence the rate and characteristics of some cardiovascular diseases, primarily a coronary and cerebrovascular disease.[1] Among the major cardiovascular risk factors, cigarette smoking and hypertension have been widely investigated with regard to their relationship with heart and blood vessels in an attempt to assess their effectiveness to impair both clinical outcome and prognosis in those patients who met these two factors, but no unanimous conclusion on the subject has been achieved.[2] Separately taken into account, there is evidence that smoking and hypertension are both independent risk factors for cardiovascular disease,[3-5] although the first factor is strongly associated with the appearance of elevated blood pressure.[6] In addition, the link between smoking and hypertension is still far to be completely identified since, usually, a smoker begins to smoke as before as the appearance of the blood pressure disorder and, therefore, confusion exists to assess whether hypertension will appear spontaneously and independently in the individuals affected or, on the contrary, is a result of smoking habit.

Whatever the assessment of hypertension is approaching, there is evidence that severe pathological alterations characterize the complications of the disease, being hypertension often asymptomatic and occasionally identified during a routine medical control. In addition, establishing the values over which blood pressure is a cardiovascular risk factor is hard, particularly when cigarette smoking is associated.[7,8] This review is aimed to separately analyze the role of cigarette smoking and hypertension as independent cardiovascular risk factors as well as their main and still debated effects when they are associated.

Cigarette smoking

It is worth noting that is appropriate to indicate the effects due to cigarette smoking when cardiovascular damage is analyzed, but not to tobacco because one of the most responsible compounds of the damage like carbon monoxide is a product of the lit cigarette, but not of fresh or manufactured tobacco leaf.[2,9] However, cigarette smoking, tobacco smoking, tobacco toxics and smoking are all used with the same meaning.

Of the over 4,000 toxic substances identified in cigarette smoking, there is evidence that mainly two, specifically nicotine and carbon monoxide, exert toxic effects on the heart and blood vessels. Both these compounds show their harmful properties by different mechanisms. Nicotine damages cardiovascular system acutely by stereoisomer and receptor binding mechanisms. The first[10] produces potent cardiovascular and sympathoadrenal effects. In addition, repeated administration of nicotine is associated with the development of tolerance as a result of the nicotine-receptorbinding.[10-12] By these processes, nicotine causes a different degree of addiction and sympathetic nervous system stimulation, increased catecholamine release and blood rheology changes with enhanced viscosity.

With regard to stereoisomery, the two isomers of nicotine have different effects according to their prevalence. Usually, Nicotine-isomer (+) exerts only poor effects on heart rate and plasma catecholamine, having, also, initially an unpleasant taste for both smokers and nonsmokers, while Nicotine-isomer (-), which is the main constituent of the nicotinic moleculeproduces more marked effects on heart rate, blood pressure via catecholamine release, and sympathetic stimulation. It is also pleasant, and this characteristic has been industrially reinforced, for smokers.[13,14]

Sympathetic nervous system stimulation mediated by nicotine determines increased heart rate and systolic blood pressure directly and as a result of increased epinephrine and norepinephrine release. The responses evoked are initially transient, but repeatable because they are maintained by catecholamine release[15-17] (Table 1).

Table 1 Main cardiovascular effects mediated by nicotine.

Sympathetic nervous system stimulation
Increased catecholamine release
Increased systolic blood pressure (acute effect)
Increased heart rate (acute effect)
Endothelial function (dysfunction)

With regard to endothelial function, there is evidence that nicotine is able to determine endothelial dysfunction by multiple mechanisms as documented by animal studies, where increased oxidative stress seemed to play a significant role. The very significant finding of Neunteufl et al.[18] contributed to clarify this topic. The authors' study concerned 60 healthy smokers who were enrolled into a randomized, observed-blinded crossover study, which compared

the effects of nicotine administration on vascular reactivity in the brachial artery. Evidence indicates that the normal response of this parameter is a well recognized target of normal endothelial function. The conclusions reached by these findings demonstrated that nicotine administered alone caused endothelial dysfunction because of an impaired endothelium-dependent vasodilation and reduced nitric oxide production.

Similar results were reported by the studies of Celermajer et al.,[19] and Giannini et al.[20] In addition a very recent review of Leone[21] gave effectiveness to these results, also discussing the role of nicotine-enantiomers. It would seem a logical assumption that a reinforced power of the Nicotine-isomer (+), having a well-known unpleasant taste in the smoked cigarette, could reduce nicotine desire and, consequently, the smoking habit. Carbon monoxide, a diatomic molecule derived from a binding of oxygen with carbon, withthe possibility of moving the atom to hemoglobin, forming carboxyhemoglobin, develops its toxic effects on the heart and blood vessels because of this chemical compound. There is overwhelming evidence that carboxyhemoglobin causes tissue hypoxia, which is the main determinant of the damage produced by carbon monoxide.

Carbon monoxide from a single cigarette achieves a small concentration in the blood and, therefore, can acutely induce functional, but transient responses, particularly documented with regard to the exercise tolerance in individuals passively exposed,[22-25] whereas dated chronic smokers usually show irreversible alterations of the heart and blood vessels.[26-28] Hypoxia is a well-documented factor for myocardial and coronary vessel lesions. Thus, the pathological alterations caused by the gas produced by cigarette smoking justify a discussion on the type of damage. A first question to be taken into account is the level of blood carboxyhemoglobin concentrations at which the hypoxia damages the heart and blood vessels. In addition, if carbon monoxide from smoking is able to reach alone these concentrations. This is a question often neglected by the large majority of papers related to carbon monoxide damage. Thus, there is evidence that the effects caused by the gas generally determine cardiovascular alterations. On the contrary, the concept to be emphasized is the role of carbon monoxide able to induce mild effects at a lower concentration up to death, also acute death, when the toxicosis produced by the gas dramatically increases.

It is worth noting that the lethal dose able to determine unpleasant effects up to acute death varies from 1-hour exposure to 1,000 to 1,200ppm, where unpleasant, but no dangerous symptoms are usually seen, to 1,500 to 2,000, which results a dangerous concentration after 1 hour of exposure. However, these investigations concern old papers, still to be taken into account, that analyze carbon monoxide derived from sources different from cigarette smoke, which does not reach similar concentrations. It is worth noting that the lethal dose of the gas is fixed at a concentration as equal as 400 parts per million air.[29] In general, a carboxy hemoglobin level of 40% is accompanied by mental confusion, added to increase of incoordination, which is preceded by prodromic symptoms, and preclude to the appearance of loss consciousness and death[30] (Table 2).

Table 2 Main effects of carbon monoxide

Removing oxygen from oxyhemoglobin
Increased carboxyhemoglobin concentrations
Tissue hypoxia

These brief observations clearly explain the reasons of why cigarette smoking cannot induce acute death because similar concentrations of the gas are unimaginable in a smoker, but, however, are able to generate hypoxia as a result of altered oxygen availability. The effects of both nicotine and carbon monoxide on the heart and blood vessels well clarify the type of damage observed in smokers, past smokers non exposed to smoking, past smokers exposed and exposed never smokers. Acute exposure to cigarette smoke usually begins with a functional, but transient alteration of the endothelium and myocardium well identified in healthy nonsmoker individuals or individuals suffering from ischemic heart disease exposed to passive smoking.

There is clinical and experimental evidence that these individuals meet endothelium-dependent vasodilation, as a result of reduced nitric oxide, and increased systolic blood pressure and heart rate.[19-21,31-37] With regard to active smokers, the evidence indicates that the major determinants of vascular damage assessed when a smoker is smoking a cigarette consist of acute changes in thrombosis parameters withthe increased aggregation and adhesiveness of platelets that may, also, display alterations in their shape.[38-40] (Table 3).

Table 3 Main determinants of the acute vascular damage from smoking.

Active smoking	Passive smoking
Increased platelet aggregation vasodilation	Impaired endothelium-dependent
Increased platelet adhesiveness	Reduced nitric oxide production
Changes in platelet form	Increased systolic blood pressure
Thrombus formation	Increased heart rate
Increased carboxyhemoglobin	Increased carboxyhemoglobin

With regard to the heart, a transient, but reduced tolerance to exercise characterize the individuals exposed to smoking either are active or passive smokers and healthy subjects or suffering from ischemic heart disease as well established by several findings.[22-25] All these studies reached the conclusion that the parameters examined were differently impaired during exercise in a smoking environment, but all constantly showing increased concentrations of carboxyhemoglobin, which was proportional to the duration of the exposure. The observations obtained undoubtedly show that endothelial damage was primarily mediated by the effects of nicotine on sympathetic nervous system and catecholamine, although increased carboxyhemoglobin concentrations had been documented. On the contrary, the acute alterations of the myocardium consisting of a reduced tolerance to exercise were under the control of carboxyhemoglobin, a parameter able to induce myocardial hypoxia.

The initially functional damage changed its characteristics at the time if the individuals continue to smoke or are constant, although irregularly, exposed to passive smoking. The pathological damage from cigarette smoke recognizes either myocardial or vascular alterations primarily involving coronary, cerebral and carotid arteries. Table 4 groups the type of clinical and pathological alterations of the heart and blood vessels caused by cigarette smoke.

From the analysis of (Table 4), there is evidence that a wide spectrum of alterations may be caused by cigarette smoking with no data of prevailing one type rather than another one. Myocardial infarction from cigarette smoking recognizes two pathogenic mechanisms: coronarogenic, related to coronary atherosclerosis and its

complication, and toxic as a consequence of a direct and toxic effect of carbon monoxide on the myocardium with or no coronary lesions.[41-46] It is worth noting that smokers have a relatively altered coagulation state as documented by increased hematocrit and fibrinogen levels. In addition, quantitative coronary angiography analysis suggests that the mechanism of infarction in smokers is more often thrombosis of a less critical atherosclerotic lesion compared with non-smokers.[47]

Table 4 Main pathological alterations of the heart and blood vessels caused by smoking

Heart	Artery vessels
Ischemic heart disease coronary atherosclerosis	
-Stable angina	
-Myocardial infarction	
-Cardiomyopathies	
-Heart failure	
-Arrhythmias	
Cerebrovascular disease	Cerebral atherosclerosis
-Ischemic stroke	
-Hemorrhagic stroke	
Hypertension	Carotid stenosis
Peripheral arteriopathies Microcirculation	
-Thromboangiitis obliterans	

Some topics of the myocardial infarction of smokers should be carefully taken into account. First, the major extent and type of coronary artery pathology.[45] Secondly, the possible appearance in subjects with normal coronary arteries as a toxic effect of carbon monoxide.[44,46] Thirdly, a major rate of myocardial infarction occurring with no chest pain,[48,49] similarly to the infarctions that may be observed in old and diabetic patients, probably because of sympathetic nervous system dysfunction.

Ischemic heart disease in smokers may display signs of heart failure of various degrees due to the development of an ischemic cardiomyopathy due to a progression of coronary atherosclerosis and degenerative alterations of the myocardial cells.[40] In addition, evidence indicates that the complex vascular pathology that affects the arterial circulation in smokers is a close result of the complications, which involve the atherosclerotic plaque.[50,51]

A short discussion is useful to be done for the micro circulatory alterations of the smokers in an attempt to better establish the morphology, significance, and progression of the arterial lesions. Microcirculation primarily involves resistance arteries and arterioles up to blood reflux in the great venous system. Both conduit and resistance arterial vessels may show vascular morphological and functional alterations due to cigarette smoking.[52] Pathological lesions involve the arterial wall or intravascular lumen with, primarily, narrowing and thrombo-embolic events as an effect of endothelial and blood cell changes related to smoking. On the contrary, functional disorders are the result of a wide spectrum of biochemical, physiological and metabolic factors. While conduit vessel alterations have been widely investigated, little is known about the changes induced by smoking on the microcirculation. It would seem that the endothelium, platelet aggregation and adhesiveness, nervous system and metabolic changes play a role in damaging resistance arteries and, then, the microcirculation.

The result of these effects changes the blood flow and perfusion particularly to the heart, brain and kidney. Alterations of the microcirculation can cause severe and widespread damage because, in addition to the complications of the atherosclerotic lesion which characterizes large arteries, there is a failure of body organs linked to the degree of microvascular damage. Moreover, it seems that 2 major compounds of cigarette smoke are capable of determining vascular damage; initially, nicotine acts preferably on large arteries and carbon monoxide on small arteries, although both compounds damage the vascular system. Analyzing the significance of the data described, there is evidence that smoking is a harmful factor of cardiac and vascular pathology at different levels, also able to significantly increase the rate of both cardiovascular disease and related nonfatal and fatal events.

Hypertension

A previous paper[53] properly emphasized that usually many reports started with, approximately, these words: "Hypertension is a major risk factor for developing coronary heart disease and stroke". This statement may seem, at a first sight, a trite sentence of introductory type, but, on the contrary, it contains the basic assumption, which defines meaningfully what is and the role of hypertension. It is worth noting that a generic title as "Hypertension" would require more than a textbook of medicine (and there are very excellent textbooks, one of the more complete of which, as first published on 1990 and, then, periodically updated[54] is that of Laragh and Brenner) in an attempt to clarify the major biochemical, physiological and pathological characteristics. This statement is not the purpose of the current review deputed, on the contrary, to shed light upon those points of view, which may be associated with cigarette smoking. Therefore, the main purpose is only to describe the effects and role of the elevated blood pressure as a cardiovascular risk factor.

The first step to be established is the normal range of blood pressure and its changes according to the current concepts, which have been modified with regard to the past. Currently, hypertension may be defined as is when stable measures over 140mmHg and 90mmHg are found in the absence of associated cardiovascular risk factors. When a cardiovascular risk factor accompanies the blood pressure, proportionally lower values are believed to fall in a normal range.[55-56] The complications, most frequently observed in hypertensive individuals (Table 5)[57] are hypertensive heart disease, coronary artery disease, stroke, aortic aneurysm, peripheral artery disease and, particularly, chronic kidney disease with a high arteriolar damage. In addition, evidence indicates that a development of chronic heart and kidney failure is a frequent end-stage in hypertensive individuals.

Table 5 Complications of hypertension

Hypertensive heart disease
Coronary artery disease
Stroke (thrombotic and hemorrhagic stroke)
Aortic aneurysm
Atherosclerotic artery disease
Chronic kidney disease
Chronic heart failure
Chronic kidney failure

A large number of epidemiological findings,[58-66] some related to cardiovascular or renal patterns, providing also effective suggestions for the treatment of hypertension, some others in the association of blood pressure with metabolic disorders, undoubtedly demonstrate the significant role of this disorder in inducing and maintain the high rate of cardiac and vascular events. However, limits regarding the absolute and relative risk of normal-high blood pressure exist, although data[58] support the hypothesis that this parameter may be associated with an increased risk of cardiovascular disease also at the mild values and, therefore, lowering normal-high blood pressure could reduce cardiovascular risk. Starting from these observations, a dramatic consequence is that even high blood pressure should be effectively reduced in an attempt to maintain cardiovascular risk at a lower rate.

As shown, both systolic and diastolic blood pressure contributes to increase the risk of cardiovascular and kidney disease, and evidence indicates that the same targets of cigarette smoke are also targets of hypertension. Therefore, optimal values with regard to blood pressure in adults should reach systolic measures of 120mmHg and less than 80mmHg for diastolic blood pressure, particularly in association with other cardiovascular risk factors.[67] Finally, the observations described undoubtedly show that hypertension is a well-known independent cardiovascular risk factor and its related-risk can be modified by appropriate lifestyle, preventive measures and pharmacological therapy, if necessary. However, the real problem is if an effective control of blood pressure may influence the spontaneous outcomes of its complications since proven results do not exist or are consistently controversial.

Combined effects of smoking and blood pressure

Hypertension has been commonly and is still considered one of the major coronary risk factors, which is often associated with others, including cigarette smoking. In addition, there is evidence that hypertension is one of the most frequent diseases and a leading cause of morbidity and mortality since it is able to cause a large variety of cardiovascular and cerebrovascular complications.[68-73] Some of these events are strongly associated with cigarette smoke, while others show to be related to the disease that high values in blood pressure can determine.

With regard to the association of cigarette smoking with hypertension, the first observation to be emphasized and still with no clear answer is to assess the time relation between these two factors. Usually a hypertensive subject, who smokes, begins to smoke before the appearance of high values of blood pressure unless in case of congenital disease or secondary hypertension. No data would permit to establish whether hypertension, primarily essential hypertension, closely depends on smoking habit or, on the contrary, will develop spontaneously as an event related to the genetic and physiological characteristics of the individual. Missing a direct evidence of this assumption, indirect observations can help to assess the role of smoking-related hypertension alone and hypertension with no relationship with tobacco smoke in both smokers and nonsmokers passively exposed.

At first, statistical reports contribute to provide this response. Active smokers usually have blood pressure, which may vary widely, although displaying a trend towards elevated values. Many factors related to lifestyle, race, and genetic predisposition play a significant role to determine the characteristics of this parameter. Studies conducted in different countries[68-69,71] showed that men who smoked had a systolic blood pressure inversely correlated to cigarette smoking. The systolic blood pressure was reduced 1.3mmHg in 1.1% of light smokers, 3.8mmHg in 3.1% of moderate smokers, and 4.6mmHg in 3.7% of heavy smokers when these individual were compared to nonsmokers. The results observed could be interpreted as an indirect manifestation of a more severe hypertension specifically related to smoking, particularly in heavy smokers, independent of the baseline values in blood pressure.

A feature to be also examined is the effect exerted on blood pressure by chronic smoking in the active smokers. According to the epidemiological reports examined,[68-71] two types of response characterize chronic active smokers: an initial phase lasting a different number of years, and a late phase following the first. The initial phase of chronic exposure to active smoking usually shows a lower blood pressure than that of nonsmokers or past smokers. This feature involves males, females and adolescents of a different race. Loss in body weight due to smoking usually is interpreted to contribute in reducing blood pressure. On the contrary, dated smokers usually develop a stable hypertension mainly due to the toxic effects of carbon monoxide.[35]

Passive smokers show a typical outcome in blood pressure depending on several factors, primarily the duration of exposure and environmental smoking toxic concentrations.[36-37] Evidence indicates that chronic exposure to passive smoking determines a hypotensive response in the first years of exposure, followed, at the time, by stable hypertension similarly to what is observed in active smokers. However, chronically exposed nonsmokers with hypotension meet a transient hypertensive response when an acute exposure again occurs[2] similarly to that of an active smoker who smokes a cigarette. A phenomenon to be emphasized is the masked hypertension due to an effect of the combined action of nicotine and carbon monoxide.

This pattern, firstly described by Leone et al.[73] as an explanatory hypothesis on the fact that no unanimous opinion supported the association of smoking with blood pressure, consists of a mechanism of hypotension regulated by the vasodilator effects of nicotine after the initial phase of the increased blood pressure that masks the potential hypertensive damage, which carbon monoxide could produce by inducing alterations in the arterial wall. The latter will be clearly manifest in the years. As previously described, endothelial dysfunction, increased arterial stiffness, and platelet function changes caused by smoking exposure contribute to increase chronically blood pressure, but are also factors strongly related to hypertension. These observations undoubtedly show a strong relationship between cigarette smoking and hypertension that, in addition, exponentially potentiate their adverse effects on cardiovascular system when they are associated.

Conclusion

A large number of observations emphasize the adverse effects of smoking and hypertension on the heart and blood vessels, both acting as independent risk factors able to increase the rate of cardiovascular disease. A close relationship exists between these two factors, although is still hard well establishing the specific role of each of them when are associated. However, evidence indicates an exponential increase in the rate of cardiovascular disease with respect to the effects of hypertension and smoking separately acting.

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