

## Morphological Alterations of the Heart and Blood Vessels from Tobacco Smoke: the Steps of the Damage

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### ABSTRACT

Two cardiovascular structures are usually involved in the harm caused by cigarette smoke: myocardium and endothelium, which are mainly affected by carbon monoxide and nicotine. The harmful effects of smoking induce functional responses that eventually lead to morphological damage. With regard to the myocardium, three main steps have been well documented: myocardial alterations related to the hypoxia caused by increased concentrations in carboxyhemoglobin, reversible degenerative alterations of the cardiac muscle and irreversible myocardial necrosis. A typical experimental pattern due to smoking effects is the smoke cardiomyopathy. Endothelial dysfunction triggers a large number of responses, mainly consisting of blood and inflammatory cell migration and adhesion at the site of altered arterial wall, rupture of the muscular and elastic cells of the arterial wall and lipid infiltrates, which lead to atherosclerosis plaque. In addition, arteriosclerosis is the result of smoking on the resistance arteries. Evidence indicates that morphological alterations of the heart and blood vessels from smoking follow a well-defined way that allow us to tell the story of the cardiovascular alterations.

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**Key words:** Morphological damage; Myocardium, Endothelium; Cigarette smoking

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### INTRODUCTION

There are many things in life that will catch your eye, but only a few will catch your heart-Winston Churchill<sup>[1]</sup>.

There is overwhelming evidence that a strong link exists between the damage caused by cigarette smoke, but not tobacco leaf, and cardiovascular system with regard to the development of morphopathological alterations. This statement is basic to be kept in mind because one of the most harmful substances like carbon monoxide is a product of the combustion of a cigarette but not tobacco plant<sup>[2-5]</sup>. Therefore, beside the positive responses, also adverse things may catch the heart as an effect of cardiovascular risk factors, including cigarette smoking, which is a completely avoidable habit<sup>[6]</sup>.

It is almost generally accepted that cigarette smoking, in both its type as active and passive smoke, exerts harmful effects on the heart and blood vessels, which are prevailing on some structures identified as target<sup>[2,7-10]</sup>. Myocardium and endothelial cells have been clearly documented to be affected with a high rate<sup>[11-20]</sup>.

The purpose of this review is to analyse the development of cardiovascular damage from cigarette smoking by telling what may be considered the basic steps of the damage

### CHARACTERISTICS OF SPECIFIC MYOCARDIAL AND VASCULAR STRUCTURES RELATED TO SMOKING

Generally, the alterations caused by cigarette smoking to the heart and blood vessels have been believed to occur occasionally. On the contrary, some anatomical and physiological characteristics would seem to explain the prevalence of the lesions at a site rather than

another one.

In the adult heart, a fibrous framework, recognized as cardiac skeleton, with function of support and attachment with the atrial and ventricular musculature, and myocardial cells allows the contractility and, therefore, the function of the structure, anatomically identified. As can be known, different metabolic and functional properties are specific of these structures of cardiac muscle.

There is evidence that myocardial cells require oxygen availability to warrant their contractility and, then, the progression of the blood to all tissue and body organs.

It is worth noting that oxygen is strongly related to the effect of carbon monoxide, which primarily produces a strong bond with hemoglobin producing carboxyhemoglobin<sup>[21-22]</sup>. Thus, this concept has to be carefully taken into account in an attempt to well understand the reasons of the different tropism towards smoking of different structures of the same organ, including the heart. Those structures at a higher metabolism undoubtedly need a maximum amount of metabolically active oxygen.

With regard to arteries, the endothelial cells, which are a structural monolayer contiguous to blood and sub-intimal coat, are affected primarily by nicotine, which stimulates both sympho-adrenergic system and endothelial metabolites with a reduction of nitric oxide concentrations and, consequently, endothelium-dependent vasodilation<sup>[23-26]</sup>.

Table 1 summarizes the main tropism of carbon monoxide and nicotine on the structures of the cardiovascular system.

As can be clearly seen, myocardial cells and vascular endothelium, which exert specific metabolic function, are the targets of those chemical smoke compounds like carbon monoxide and nicotine able to cause cardiovascular damage.

## FROM FUNCTIONAL TO MORPHOLOGICAL DAMAGE

Two types of cardiovascular damage have been documented as a result of cigarette smoking effects. A first type consists of a functional damage initially transient, but repeatable that, in the long run, produces a stable anatomical alteration of the cardiovascular structures affected<sup>[27-30]</sup>. In addition, there is evidence that the two types of damage can, sometimes, co-exist primarily in those subjects exposed frequently to passive smoking either healthy subjects or subjects suffering from ischemic heart disease<sup>[31]</sup>.

The functional damage (Table 2) is characterized by reduced tolerance to the exercise and myocardial hypoxia due to the increased concentrations in carboxyhemoglobin. With regard to artery vessels, endothelial dysfunction accompanied by reduced nitric oxide production and impaired endothelium-dependent vasodilation typically occur.

Functional damage affects both active and passive smokers when they touch with the smoking habit. Several mechanisms related to endocrine and sympathetic nerve stimulation, reduced oxygen availability and blood marker changes<sup>[32]</sup> activate and support its

occurrence. The stable changes in endothelial function are the line of separation between functional and starting pathological changes.

The necessary steps that lead to morphological damage involve the myocardium and artery vessels by different lesions and mechanisms related to direct and mediated action of smoking toxics, as table 3 shows.

As William Osler literally wrote<sup>[33]</sup>: “The subjects of angina are often men accustomed to eat freely of rich foods. Angeio-sclerosis is the Nemesis through which nature exacts retributive justice for transgression of her laws.”, According to the progress of our knowledge, there is evidence that also other risk factors, including cigarette smoking and, perhaps hypertension should have to be considered in this statement, which underlines almost exclusively features, related to metabolic factors.

Findings, conducted either clinically or experimentally on both humans and animals, allow us to well recognize the morphological damage caused by cigarette smoke primarily in some structures of the heart and blood vessels. The alterations observed are undoubtedly the result of the combined action of nicotine and carbon monoxide, although the latter has to be considered the main promoter of the pathological damage by a direct mechanism.

## MORPHOLOGICAL FEATURES OF CARDIOVASCULAR DAMAGE FROM SMOKING

There is evidence that cardiovascular damage from smoking begins as early as an individual smokes the first cigarettes, and progressively continues<sup>[34]</sup>.

As an individual inhales cigarette smoke, a great amount of toxic for cardiovascular system and primarily carcinogens, a great number of these water-soluble, flood mainly some body organs like lung, heart and epithelial glands identified as target of smoking. The truth

**Table 2** Typical patterns of functional damage affecting cardiovascular system.

Heart	Transiently reduced tolerance to the exercise; Myocardial hypoxia; Reduced oxygen availability.
Blood vessels	Reduced nitric oxide production; Impaired endothelium-dependent vasodilation.

**Table 3** Pathological alterations due to cigarette smoking.

Heart	Myocardial cell alterations; Myocardial necrosis; Myocardial fibrosis; Intracellular ultrastructural changes; Cardiomyopathies.
Artery vessels	Inflammatory process of the endothelial cell; Degenerative alterations in the arterial wall; Fibrosclerotic alterations in the arterial wall; Atherosclerotic plaque and its complications.

**Table 1** Main tropism of carbon monoxide and nicotine on cardiovascular system.

Chemical	Heart	Artery vessels
Carbon monoxide	Myocardial cells; Carboxyhemoglobin.	Endothelial cells; Carboxyhemoglobin. Reduced nitric oxide;
Nicotine	Increased heart rate; Increased blood pressure; Increased contractility.	Impaired endothelium-dependent vasodilation; Increased hemodynamic responses; Sympathetic nervous system stimulation; Adrenergic stimulation.

is, for all its declining popularity, smoking still emerges as the single greatest preventable cause of death in the United States. Each year, more than 3 Million people currently die as an effect of smoking exposure, half of them before the age of 70 years<sup>[2,35-36]</sup>.

Morphological damage from cigarette smoke follows a way today well identified and this permits to build the true story of the damage.

Initially, morphological alterations from smoking are caused by a mechanism due to hypoxia as an effect of carboxyhemoglobin produced by carbon monoxide, which removes the bond between oxygen and hemoglobin for the myocardium, and post-endothelial dysfunction mediated by nicotine<sup>[37-41]</sup>.

Two types of myocardial cell alterations may be induced by hypoxia: acute pathological changes that can lead to myocardial necrosis, and chronic degenerative alterations, which can cause a cardiomyopathy.

With regard to endothelial activation, a large number of effects may be seen, going from the blood and inflammatory cell migration and adhesion to the site of the altered artery wall to degenerative phenomena consisting of muscle and elastic fiber fragmentation and lipid infiltrates along the arterial wall. There is evidence that endothelium-derived nitric oxide could modulate leukocyte adhesion, but, as aforementioned, a reduced production is a typical pattern of endothelial dysfunction, usually preceding endothelial activation.

This step, which characterizes the initial morphological lesions of the heart and blood vessels caused by carbon monoxide and nicotine, continues to follow a typical way consisting in the progression of cardiovascular lesions up a level, which is the limit between reversible and irreversible cardiovascular lesions primarily for those smokers who do not quit smoking<sup>[42-45]</sup>.

It is worth noting that the occurrence of irreversible alterations immediately follows the previous step and consist of necrotic and degenerative patterns for the myocardium, and atherosclerotic plaque formation for the arterial vessels, as table 4 shows.

Myocardial necrosis is the most serious event met from the smokers and nonsmokers frequently exposed passively.

Since this pathological pattern may occur with both a vascular and toxic mechanism, an explanation of terms is useful to be conducted in an attempt to avoid confusion in those subjects affected who do not display coronary pathology.

Necrosis is defined as the result of morphological changes, which lead to cell death. The cells, which are affected, are completely unable to play their function<sup>[46]</sup>.

Usually, necrosis from cigarette smoking recognizes both the mechanisms, the vascular and toxic, because coronary atherosclerosis occurs with a high rate in smokers being also characterized by a major extent in vessel narrowing and number of arteries affected<sup>[17]</sup>.

When these two mechanisms of damage co-exist myocardial necrosis feels the effects of both carbon monoxide for coronary and myocardial lesions and nicotine to a limited degree for the toxic features. Therefore, beside the classical colliquative myocytolysis, coagulation necrosis, recognized by the appearance of contract bands, may be seen. Usually, the latter is the result of catecholamine

stimulation probably mediated by nicotine<sup>[47-52]</sup>. However, when myocardial necrosis affects a smoker, the role of cigarette smoke should be taken into account.

A typical evidence of myocardial cell damage experimentally induced by cigarette smoking is the smoke cardiomyopathy.

Lough<sup>[53]</sup>, Gvozjakova *et al*<sup>[54]</sup>, and Kjeldsen *et al*<sup>[38]</sup> described this pathological condition in different animal species. It consisted of experimental and reproducible alterations, observed microscopically and ultrastructurally, of the myocardium, which displays myocytolysis, non-ischemic necrosis, hyalinosis, inflammatory foci, calcification and fibrosis. However, the very typical lesions of the smoke cardiomyopathy consist of hemorrhagic foci localized in the interstitium and around intramyocardial small arteries due to the toxic effects of carbon monoxide.

Finally, a short comment has to be made with regard to the artery wall alterations in the great (conduit) and resistance (microcirculation) arteries. The alterations caused by cigarette smoking recognize a similar mechanism, but differ in the characteristics of damage because of the structure of the artery wall<sup>[55]</sup>, primarily muscular and elastic in the conduit vessels versus a significant reduction in these components of the resistance arteries and arterioles.

Both conduit and resistance arterial vessels may show vascular morphological and functional alterations due to cigarette smoking. 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. 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 inducing, at the end, the arteriosclerotic lesion. 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.

## CONCLUSION

In conclusion, there is no doubt that cigarette smoking is a major cardiovascular risk factor able to cause severe morphological alterations in myocardial and vascular cells of both humans and experimental animals. Structural changes also involve intracellular components like mitochondria, ribosomes, and nuclear particles with deep alterations of enzymatic respiratory chains<sup>[21]</sup>.

A functional damage triggers the morphological alterations, which recognize three main phases. An initial and intermediate phase where the alterations of the myocardium and vascular endothelium are reversible in presence of quitting smoking, and a phase of irreversible morphological lesions consisting of myocardial necrosis and cardiomyopathies that can lead to heart failure, as well as the development of atherosclerotic plaque often complicated by rupture and thrombus-embolic phenomena.

Nowadays, a well-known way of the morphological steps of cardiovascular damage permits to tell the story of the characteristics and localization of cardiovascular damage from cigarette smoking.

**Table 4** Irreversible morphological alteration from smoking.

Heart	Myocardial necrosis; Cardiomyopathies (clinical and experimental); Heart failure; Arrhythmias.
Artery vessels	Atherosclerosis and its complications; Arteriosclerosis (microcirculation); Aortic aneurysm; Peripheral artery disease.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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