

Relationship Between Cigarette Smoking and Other Coronary Risk Factors in Atherosclerosis: Risk of Cardiovascular Disease and Preventive Measures

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Abstract: Among the major Coronary Risk Factors (CRF) cigarette smoking has shown undoubtedly harmful effects on the heart and blood vessels either as active smoking (smoking a cigarette) or passive smoking (exposure to environmental tobacco smoke -ETS). The strong relationship between cigarette smoking and cardiovascular disease has been seen independent of the other CRF in a number of well-designated epidemiologic studies. However, a strong increase in the excess of cardiovascular risk has been defined along with the interaction of cigarette smoking and other major CRF.

Thousands of pharmacologically active substances are present in tobacco smoke, and a large number of direct and indirect effects have been demonstrated. Different responses are also related to these types of exposure: active exposure or passive exposure. The cardiovascular risk increases with increasing levels of blood pressure and/or serum cholesterol and diabetes mellitus, and at each level of these three risk factors, distributed with different rates according to age and gender in individuals, the risk in active smokers or passive smokers is greater than the risk in nonsmokers.

Further analytical and methodological observations are needed for better understanding of the chemical and biological synergism. Nevertheless, evidence is clear that cigarette smoking greatly increases the risk of cardiovascular diseases in individuals already at increased risk because of other CRF.

Preventive measures must be absolutely conducted to prevent the CRF interaction. These are the changes in lifestyle (i.e. to give up smoking and make physical activity), drug administration, diet supplementation especially by those substances with antioxidant effects.

BACKGROUND

Smoking is on of the major cardiovascular risk factors able to cause harmful effects on the heart and blood vessels as well as endothelial dysfunction, an early key event in atherogenesis [1]. A large series of study [2-37] have undoubtedly shown that both active smoking and/or passive smoking can cause severe cardiovascular alterations.

Previous findings [4-5; 10-19; 21-23; 35] supported the above statement allowing to formulate the "Theorem of Leone" [35]: Active smoking injures the cardiovascular system chronically, causing structural lesions, which become, in the long run, irreversible alterations mainly related to coronary atherosclerosis. In contrast, passive smoking causes transiently impaired cardiac performance which may be considerably harmful for those people with established ischaemic heart disease."

Several aspects, which concern the mechanisms of damage from smoking, are yet not known. Among these is the cause of endothelial dysfunction in smokers. Increased oxidative stress might reduce the bioavailability of endothelium-derived nitric oxide, leading to impairment in vasodilator

response [38]. Previous findings seem to suggest that smoke-related endothelial dysfunction is potentially reversible after withdrawal from active or passive smoking [39-40].

This review will describe the effects of active smoking (chronic exposure), passive smoking (acute environmental exposure), interaction between cigarette smoking and other major CRF, preventive measures to reduce cardiovascular alterations due to combined action of smoking and the other CRF.

ACTIVE SMOKING (CHRONIC EXPOSURE)

Our previous studies consisted of 2,679 subjects (Table 1).

Subjects were outpatients who were smokers and/or nonsmokers as a control group, patients who survived the first acute myocardial infarction (some of them gave up smoking, while others continued to smoke), and autopsy cases, both smokers and nonsmokers, who died of acute myocardial infarction in Coronary Care Unit.

Clinical and electrocardiographic signs of myocardial ischaemia [10-11] were seen in a large majority of smokers when they were compared with control nonsmokers ($P < .01$, a statistically significant difference).

Leone *et al.* [16] also analysed the long-term prognosis of smokers who survived the first acute myocardial infarction. The end-points of this study were reinfarction and

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Table 1. Active Smoking. Study Material

Subjects (total=2,679)	Number	Type of myocardial damage
1. Out-patients	1,432	
Ever Smokers	1,232	Clinical
Never Smokers (control group)	200	Clinical
2. Smokers with a previous AMI	1,167	
Stopping Smoking	724	Clinical/Anatomical
Continuing Smoking	443	Clinical/Anatomical
3. Autopsy Cases	80	
Ever Smokers	68	Anatomical
Never Smokers (control group)	12	Anatomical

AMI= Acute Myocardial Infarction.

death. These findings did evidence a statistically significant increase of reinfarctions in those people who continued to smoke after their infarction compared to those who stopped smoking after their infarction. On the contrary, the deaths, after a mean five-year follow-up, were similar for the two groups.

For smokers, who survived the first acute myocardial infarction, greater mortality was supported in other studies. Pohjola *et al.* [25] in a study of men who survived for one year after the first acute myocardial infarction reported that age-adjusted deaths in the next four years were 2.3 times greater for continuing smokers than for nonsmokers. In those subjects who stopped smoking after the attack, the risk was almost identical with that of the nonsmokers. One of the major large study on cardiovascular diseases – the Framingham Study [26] - showed that those people who stopped smoking after a heart attack had a death rate 6 years later that was 62 percent less than that those who continued to smoke, despite the fact that both smokers and nonsmokers still continued to have an equal number of non-fatal heart attacks. Wilhelmsson *et al.* [27], in a study on patients, who survived the first acute myocardial infarction and whose smoking habits were measured 3 months after entry, found a halving of cardiovascular mortality and non-fatal myocardial infarction over a 2-year period in those who stopped smoking. The findings of Daly *et al.*, Jenkins *et al.*, and Vlietstra *et al.* [28-30] reached similar results, although with differences in rates of mortality, reinfarction and smoking habits of the examined subjects. However, all these studies showed a cardiovascular damage from active smoking with a prevalence of ischaemic heart alterations. Our findings showing similar death rate in continuing smokers and stopping smokers after the first acute myocardial infarction could be explained by the fact that the deaths were due to the myocardial infarction itself. On the contrary, the higher incidences of reinfarction could be a consequence of coronary atherosclerosis progression due to active smoking. Confirming such a hypothesis, findings [19] conducted on continuing smokers, who survived the first acute myocardial infarction, showed a statistically higher incidence of reinfarction but not death in heavy smokers than those who smoked less.

Among ischaemic heart disease acute myocardial infarction, reinfarction and chronic angina [31], which recognize as a pathogenetic mechanism the progression of coronary atherosclerosis, are closely related to cigarette smoking than sudden death and coronary vasospasm [2], where functional disorders are frequently involved. In necropsy findings of Leone *et al.* [15] and Auerbach *et al.* [32] more advanced narrowings of coronary arteries characterized the smokers, particularly heavy smokers when compared to nonsmokers. Smoking could promote the formation of fatty plaques on the surface of blood vessels and thickening of the small coronary vessels.

Cardiovascular diseases related to cigarette smoking according to their rates of correlation, adjusted for age and other major CRF, are shown in Table 2.

Table 2. Cardiovascular Disease Related to Cigarette Smoking

(Rate listing adjusted per age and other major CRF)	
1.	Hypertension
2.	Coronary Heart Disease
3.	Cerebrovascular Disease plus Stroke
4.	Arrhythmias
5.	Aortic Atherosclerosis
6.	Atherosclerotic Peripheral Vascular Disease
7.	Thromboangiitis Obliterans (Buerger's Disease)
8.	Aortic Aneurysm
9.	Cardiomyopathy

Therefore, active smoking provides undoubtedly the strongest and most consistent correlation with the increased incidence of atherosclerotic disease and appears to be a major contributor to increased risk of disease, often in combination with other CRF.

In conclusion, there is no doubt that active smoking causes heart and vessel disease. The mechanisms, which may be raised to explain the type of damage, are lesions of the blood vessels and myocardium mediated directly by carbon monoxide [15, 18, 24], and functional disorders mediated by nicotine [18, 23]. Tables 3 and 4 show the major effects of carbon monoxide and nicotine on cardiovascular system. Carbon monoxide seems to impair cardiac response acting both directly by structural alterations and indirectly by interference with oxyhaemoglobin. Nicotine exerts its effects by stimulating sympathetic system.

Table 3. Effects of Carbon Monoxide on the Heart

A. Direct Effect (Ultrastructural Changes)
1. Damage of myocardial mitochondria
2. Myocardial focal areas of necrosis
3. Perivascular Infiltrates
4. Punctate Haemorrhage
B. Indirect Effect (Functional Changes)
1. Insufficient oxygen transportation
2. Hypoxia

Table 4. Effects of Nicotine on Cardiovascular System

1. Increased Blood Pressure
2. Increased Heart Rate
3. Reduced Left Ventricular Performance
4. Increased Levels of Catecholamines
5. Changes in LDL-Cholesterol Levels
6. Changes in HDL-Cholesterol Levels
7. Reduced Ventricular Fibrillation Threshold
8. Increased Platelet Adhesiveness
9. Increased Free-Radicals
10. Electrocardiographic Changes

PASSIVE SMOKING (ACUTE EXPOSURE AND EXPERIMENTAL OBSERVATIONS)

Observations about passive smoking as a factor, which causes cardiac impairment, have appeared in the last twenty years. A large series of observations, particularly the experimental observations deriving from acute exposure to ETS confirm more and more that passive smoking must be considered a risk factor for the development of cardiovascular disease [36].

Indoor atmosphere and confined spaces are often polluted by tobacco smoke which is inhaled involuntarily by both smokers and nonsmokers. The smokers increase the damage caused by their active smoking, whereas the nonsmokers are damaged against their will.

Most of the smoking pollutants arise from that phase of smoke defined as sidestream smoke. It contains greater concentrations of many smoke constituents (including carbon monoxide), which are, however, diluted in a large volume of air. Other two phases characterize ETS: mainstream smoke and vaporphase. The mainstream smoke is inhaled and exhaled by the smoker, whereas vaporphase is constituted by those cigarette components that diffuse through cigarette paper into the environment [41].

Experimental, epidemiological, and clinical studies conducted on humans and animals following acute or chronic exposure to passive smoking allow certainly to confirm the harmful effects on heart and blood vessels with evident changes in endothelial and platelet function as well as impairment in cardiac performance [5]. Coronary heart disease rate in nonsmokers from passive smoking shows a statistical increase in several long-term studies conducted on women married to smokers or ex-smokers as well as people living with smokers [42 - 48]. However, two studies [49-50] did not reach the same conclusions.

Exposure of a subject to passive smoking, however, should be less harmful than that to active smoking. Table 5 shows the main effects of exposure to passive smoking. Initially, ETS exposure causes primarily irritant effects such as rhinal and ocular burning. It is also well recognize that lung cancer [51] and myocardial infarction [33] can be a consequence of ETS exposure. Two main considerations arise from understanding of the effects of passive smoking on the health: the possibility of evaluating the type of damage, and legal consequences due to harmful effects on nonsmokers.

Table 5. Effect of Exposure to Passive Smoking

1. Acute Exposure
Conjunctival and rhinal burning
Cough
Impaired cardiac performance
Endothelial dysfunction (transient)
2. Chronic Exposure
Acute respiratory illnesses
Chronic respiratory symptoms
Lung cancer
Myocardial infarction
Atherosclerosis

Our findings [4-5] demonstrated negative effects of passive smoking on the heart after acute exposure in healthy volunteers and, particularly, in those people who suffered from established ischaemic heart disease. Cardiac performance was impaired heavily after ETS exposure during exercise stress testing.

Endothelium alterations due to ETS exposure are to be considered.

During the past two decades, it has been well established that vascular endothelium [52] plays a pivotal role in maintaining vascular tone. Findings lead to establish that endothelial dysfunction is an early marker of impending

atherosclerosis. Evidence indicates that the relationship between endothelium-dependent vasodilation and ETS exposure is characterized by a negative response in endothelium-dependent vasodilation in healthy people [53-55]. Endothelium-dependent vasodilation is an important marker of endothelium integrity and relates to release of endothelium-derived nitric oxide. It may be impaired by atherosclerotic process, smoking, and, probably, by several other major CRF [41, 56-57]. Endothelial dysfunction with impaired endothelium-dependent vasodilation due to ETS exposure of healthy volunteers was recently found also by Giannini *et al.* [58].

A lot of biochemical, metabolic, and structural alterations that are due to ETS exposure and able to damage heart and blood vessels have been described, some well documented and some to be under control.

Prolonged exposure to carbon monoxide has been shown to induce ultrastructural changes in myocardium (Table 3) and may account for adverse effects of ETS exposure on mitochondrial function [59-61].

The increase in platelet aggregation is another way by which ETS exposure may lead to coronary events. Platelets, which are important for the normal process of hemostasis, when activated, play a major role in thrombi formation with growth and progression of atherosclerotic plaques [62].

Elevation in plasma lipid levels, conversion of low-density lipoprotein to oxidized low-density lipoprotein, and changes in lipoprotein distribution, documented in active smokers, are not clearly demonstrated after ETS exposure.

Finally, free radicals are highly reactive oxygen products [63-64] that are extremely detrimental to the heart muscle cell membrane inducing heavy alterations in its function. Passive smoking worsens the outcome of an ischaemic heart attack through the increase of free radicals during reperfusion injury. Therefore, ETS exposure significantly worsens reperfusion injury.

People with established ischaemic heart disease often had increased levels of carboxyhaemoglobin [5], and then less capacity in oxygen transportation.

Although a large series of findings demonstrates undoubtedly the harmful effects of ETS exposure on the heart and blood vessels, opinions on the subject are not unanimous. The differing opinions about the risks to heart and blood vessels following passive smoking exposure may be the consequence of a wrong approach to the problem.

Several variables may interfere with experimental procedures. Some of these are related to smoking, some to the environment, and some to the studied subject. The main variables are listed in table 6. Indicating the above parameters – smoking, environment and subject – by the letters a, b, and c as well as n being equal to the number of variables [65], we may build the mathematical equation of cardiovascular damage from smoking. It may be formulated as follows:

$$p = \frac{(a + b + c)^n}{abc}$$

where p is the possibility of mathematical combinations.

Table 6. Variables to Assess the Damage from Passive Smoking

(Building a Mathematical Equation)	
1. Smoking	Type of inhalation Duration of exposure Harmful components (concentrations) Type of damage (Anatomical, Functional, Transient, Combined)
2. Ambient atmosphere	Climate Work Other
3. Subject	Health status Age Sex Risk factors Drug administration Diet

These large number of possible combinations may lead to different results observed in different studies. When we standardize these variables, damage to the heart and blood vessel is the result of the degree of ETS exposure, type of exposure, and presence and/or combination of the above variables. While we can argue about the degree of damage caused by ETS exposure on the heart and blood vessels, we cannot deny the evidence of its occurrence.

INTERACTION BETWEEN CIGARETTE SMOKING AND OTHER MAJOR CORONARY RISK FACTORS

Findings and controlled trials have identified cigarette smoking as an independent risk factor against the heart and blood vessels. However, it interacts with other major CRF [66-70].

Increasing levels of blood pressure or serum cholesterol increase cardiovascular risk in smokers, and at each level of these two risk factors the risk in smokers is statistically greater than in nonsmokers.

Pooling Project results [68] provide also the evidence for a synergistic effect of cigarette smoking with hypertension and elevated cholesterol levels.

Also other studies did confirm this synergism. In the Ni-Hon-San study, for example, the effect of cigarette smoking on ischaemic heart disease incidence in the presence of hypercholesterolemia appeared to be more than additive in the Japanese Americans who lived in Hawaii. The same effect was not observed in Japanese men living in Japan, who usually had lower serum cholesterol levels [69]. Evidence of synergistic effects was seen in the Stockholm prospective study [66] and the Goteborg studies [70]. The synergistic interaction among all the major CRF could explain a different cardiovascular disease rate in those people having a genetic protection against one or more CRF when compared to those who have no such state.

Multiple logistic equations have been prepared and applied to evaluate the degree of interaction of the major CRF. These equations consider the presence of multiple risk factors with additive effects within themselves. Therefore, this type of evaluation can lead to an overprediction of cardiovascular events to be expected in a population on the basis of smoking habits when that population has low levels of one or more other risk factors.

Analytical and methodological refinements appear to be useful for a better understanding of CRF synergism. Nevertheless, the evidence exists that cigarette smoking greatly increases the risk of cardiovascular events in individuals already at increased risk because of other risk factors.

The interaction between cigarette smoking and other CRF in women needs some consideration. There is clear evidence that a combination of cigarette smoking with the use of oral contraceptives potentiates the occurrence of ischaemic cardiac events.

Users of oral contraceptives were at a greater risk in our studies [12-13]. Oral contraceptives, a practice involving a large number of women in the developed countries, can cause especially deep vein thrombosis and pulmonary embolism. The use of oral contraceptives is also associated with an increased risk of thromboembolism after surgery. Thromboembolic and haemorrhagic strokes have been demonstrated in users. One of the two cases of our observations [12] was characterized by massive transmural myocardial infarction and severe coronary narrowing in a young woman – 35 year old -, who smoked 35 to 40 cigarettes per day and used oral contraceptives. This patient, who had exertional angina and silent myocardial ischaemia detected by Holter monitoring, was admitted to the Coronary Care Unit for unconsciousness due to ventricular fibrillation. After repeated direct-current cardioversions that restored sinus rhythm, acute myocardial infarction was seen at the electrocardiogram. The patient died four days later and autopsy showed the above structural alterations of the heart. The use of noncontraceptive estrogens was not associated with an excess risk of acute myocardial infarction in a study of Rosemberg *et al.* [71]. Furthermore menopausal estrogen therapy has been associated with a protective effect from ischaemic heart disease death [72].

However, further investigations need to evaluate this phenomenon. Certainly, a higher number of cardiovascular events occur in women who smoke cigarettes and also have other CRF including the use of oral contraceptives.

No individual risk factor is essential or sufficient in the onset of cardiovascular events. Usually, a multifactorial etiology may be recognized for cardiovascular disease. Thus, multivariate risk factor assessment provides useful measures of the joint level by risk factor alone or combined with others. CRF multivariate analyses permit a better understanding of the pathogenesis of cardiovascular disease giving also guidelines for their prevention.

PREVENTIVE MEASURES

Preventive measures must face towards at least three ways: lifestyle changes, drug therapy conducted against documented risk factors, and diet supplementation (Table 7).

Table 7. Main Preventive Measure to Fight CRF

1. Lifestyle Changes	Stopping Smoking Physical Activity
2. Drug Therapy against CRF	Reducing Cholesterol Level Control Hypertension Control Diabetes Mellitus Reducing Obesity Post-menopausal therapy (??)
3. Diet Supplementation	Vitamin C Vitamin E Other Antioxidants

Lifestyle changes must be done by two main ways: smoking cessation and physical activity.

Nothing less than absolute cessation of smoking and other tobacco use is needed to prevent cardiovascular events. The risk of a recurrent event in a patient with pre-existing myocardial infarction is strikingly reduced by smoking cessation. The relative risk of cardiovascular disease declines nearly to that of a nonsmoker in an year or less [73]. It is also well estimated that a 35-year-old who quits smoking extends survival by 3 to 5 years [74], with much of the improved life expectancy caused by a reduction of cardiovascular events.

Techniques for smoking cessation are more and more studied and applied to smokers [75], although with not encouraging results.

Physical activity is the second way to improve the benefits caused by smoking cessation. Moderate-intensity exercise reduces atherosclerosis progression, causes arterial vessel dilatation, and determines a fall in body weight of the smoker, who, because of smoking cessation, tends to increase its body weight. However, established results on the role of physical activity are not completely clarified. Higher levels of physical fitness and leisure-time physical activity would seem to be associated [76] with lower rates of all-cause mortality, independent of other risk factors.

Beneficial effects of drug therapy against the other major CRF are more and more well established. The other articles in this issue clarify the main aspects of the treatment of different CRF. However, hypertension, elevated serum LDL-Cholesterol, Diabetes Mellitus, Obesity, and may be, post-menopausal status should be treated in an attempt to reduce the powerful of major CRF interaction.

Finally, diet supplementation needs some consideration.

The composition of the diet has different effects on individuals metabolism with regard to their components. The most important dietary factors affecting the metabolism are fat and cholesterol. However, carbohydrate also plays a role. However, the purpose of dietary measures is to reduce the risk in cardiovascular events for those people affected by major CRF without lowering the caloric level that is needed by the subject.

Different dietary interventions have been suggested to control CRF interaction. According to clinical and/or metabolic characteristics of the subject, a dietary intervention may be chosen rather than another. The single type of diet to be followed by patients is not the purpose of the present article.

Its aim is to discuss and recommend some diet supplementations that seem to be a useful method to fight CRF interaction.

Epidemiologic studies have shown that plasma levels of antioxidant nutrients, particularly vitamins C and E, were found significantly lower in smokers compared with nonsmokers [77]. Moreover, endothelium-dependent vasodilation in the forearm circulation of chronic smokers can be improved by acute intraarterial administration of vitamin C [78]. In the Health Professionals' follow-up study, a reduction in major coronary events among healthy male subjects taking 100 to 250 IU vitamin E supplementation per day was reported [79]. In contrast, no results were seen in another randomized trial [80]. In a little group of subjects [81] oral supplementation of vitamin E could attenuate transient impairment of endothelial function after heavy smoking as a consequence of an improvement of the oxidative status but not chronic endothelial dysfunction.

These observations demonstrate that antioxidant nutrients, such as vitamin C and E, can improve endothelial dysfunction from cigarette smoking, although transiently. However, the mechanism able to cause this phenomenon is yet unknown.

CONCLUSION

Interaction between different major CRF is undoubtedly well established. That is responsible for multifactorial pathology that characterizes several cardiovascular diseases. Since a decreased cardiovascular risk is widely documented by preventive measures that can fight CRF detrimental effects, efforts must be conducted attempting to put these measures into action.

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