

Editorial

Modifying Cardiovascular Risk Factors: Epidemiology and Characteristics of Smoking-Related Cardiovascular Diseases

Smoking appears to be always the most harmful risk factor for heart and blood vessels being targeted by some of the organs tobacco components [1-3]. Of these, primarily nicotine and its metabolites and carbon monoxide, the latter is not a product of tobacco fresh leaf but develops from lit cigarette, are strongly associated with the damage of cardiovascular system.

Generally, the reviews on tobacco smoke indicate the damage caused by cigarettes and lacking the systematic findings on the harm caused by pipe or cigar smoking that are common industrial products of tobacco [4]. In addition, a question that needs some clarifying concepts is: what is the definition of tobacco smoke and what is the socio-cultural dimension of the association of smoking with cardiovascular risk?

The review of Leone *et al.* [5] discusses the subject.

The common definition of smoking as the inhalation of the smoke of burned tobacco that may occur occasionally or habitually as a consequence of a physical addiction to some chemicals, primarily nicotine, cannot be fully accepted today since several clinical, biological, metabolic, epidemiologic, statistic and socio-economic factors that play a basic role in determining individual damage due to smoking are missing in this assessment.

The analysis of findings shows undoubtedly that several constituents of cigarette smoking play a strong role in the development and progression of cardiovascular damage, primarily atherosclerotic lesions.

Nicotine and its metabolites, carbon monoxide and also thiocyanate seem to be the most specific markers of damage that, in the time, becomes irreversible.

Cigarette smoking is addictive because of nicotine and nicotine withdrawal causes many side effects of quitting smoking and usually increases cardiovascular risk.

Therefore, what is smoking?

Smoking must be defined as a chemical toxicosis which is able to cause detrimental effects either of acute or chronic type on different structures of the body like cardiovascular system, respiratory system and epithelial glands target organs. In addition, smoking causes physical addiction, primarily due to nicotine, that adversely influences smoking cessation.

From these observations there is evidence that a large number of socio-economic and epidemiologic implications arise in smokers and that require the necessity of specific structures which may help to face up the problem.

A large number of findings relate smoking to other major cardiovascular risk factors and, among this, hypertension plays a strong role that increases the harmful effects caused on cardiovascular system by smoking. However, there is no unanimous opinion on the interaction blood pressure and smoking [6-10].

Some reports identified that cigarette smoking in males was inversely related to systolic BP with, when compared to non-smokers, a reduction of 1.3 mmHg in 1.1% of light smokers, 3.8 mmHg in 3.1% of moderate smokers and 4.6 mmHg in 3.7% of heavy smokers. There was no clear relation with diastolic blood pressure. This finding was conducted in an oriental population enrolled in the study, but also in western countries blood pressure reduction was observed primarily in young smokers. In addition, some epidemiologic surveys [7, 9, 10] demonstrated that individuals who smoked a different number of cigarettes had lower blood pressure than that of non-smokers. Such a characteristic occurred in males, females, adolescents, adults and different races. However, this observation was attributed primarily to chronic smoking. There was opinion that associated loss in body weight of active smokers contributes to lowering BP.

Such data contrast strongly with the results obtained in active smokers while they are smoking cigarettes as well as in dated chronic smokers [6, 11-14].

These individuals displayed an evident increase in blood pressure that seemed to be clearly related to the toxic effects of nicotine and carbon monoxide of acute type but, particularly for what concerns carbon monoxide, also of chronic type with structural arterial lesions associated.

The review of Virdis *et al.* [15] analyzes the relationship between smoking and hypertension in an attempt to clarify this subject.

Authors underline that cigarette smoking is a powerful cardiovascular risk factor and smoking cessation is the single most effective lifestyle measure for the prevention of a large number of cardiovascular diseases. Impairment of endothelial function, arterial stiffness, inflammation, lipid modification as well as an alteration of antithrombotic and prothrombotic factors are smoking-related major determinants of initiation, and acceleration of the atherothrombotic process, leading to cardiovascular events. Cigarette smoking acutely exerts an hypertensive effect, mainly through the stimulation of the sympathetic nervous system. Concerning the impact of chronic smoking on blood pressure, available data do not put clearly in evidence a direct causal relationship between these two cardiovascular risk factors, a concept supported by the evidence that no lower blood pressure values have been observed after chronic smoking cessation. Nevertheless, smoking, affecting arterial stiffness and wave reflection might have greater detrimental effect on central blood pressure, which is more closely related to target organ damage than brachial blood pressure. Hypertensive smokers are more likely to develop severe forms of hypertension, including malignant and renovascular hypertension, an effect likely due to an accelerated atherosclerosis.

Since there is evidence that a currently largest meta-analysis [16] suggests that patients at risk of fatal or nonfatal cardiovascular events receive benefit from antihypertensive therapy regardless of baseline blood pressure and to prevent vascular events. Lowering the blood pressure is the main goal to reach more than the choice of antihypertensive drug class, we can deduce that the interaction of smoking and hypertension should also be carefully interpreted to obtain the most effective lowering in blood pressure.

The interaction between smoking and blood pressure involves a great number of epidemiological, biochemical and physiological features that, usually, are common to the mechanism of action of other major coronary risk factors [17].

Usually, atherosclerotic plaque is strongly associated with lipid metabolism changes. In addition, atherosclerotic plaque instability, commonly named vulnerable plaque, easily undergoes the rupture that is more frequently when plaque volume is bigger and macrophage content [18] and LDL-Cholesterol are elevated. However, the relationship between incidence of coronary events and lipid metabolism

changes, particularly in cholesterol concentrations, is yet far to be fully clarified as well as the role of statins in those individuals with other major coronary risk factors associated like cigarette smoking and, at the same time, treated by specific therapy. A recent metaanalysis [19] conducted to assess the quantitative relationship between triglyceride concentrations in blood and cardiovascular risk reached interesting results to be discussed. Data concerning 2 perspective large-scale trials together with other smaller studies including 262,525 individuals with a mean of 4% of nonfatal and fatal coronary events showed that there was a correlation between cardiovascular risk and level of triglycerides. Risk further increased when HDL-Cholesterol had lower values.

Starting from these concepts, the review of Gastaldelli *et al.* [20] is worthy to be carefully analyzed since it identifies those factors that link smoking and lipid metabolism.

Current epidemiological and pathophysiological evidence link smoking with cardiovascular and metabolic diseases. Among the effects of smoking there is the alteration of lipid metabolism through the increase in lipolysis, insulin resistance and tissue lipotoxicity. Smoking is both prothrombotic and atherogenic. As an effect, the risk of acute myocardial infarction, sudden cardiac death, stroke, aortic aneurysm and peripheral vascular disease is increased.

Even very low doses of exposure increase the risk of cardiovascular disease and metabolic alterations. On the other hand, smoking cessation restores, at least in part, lipid metabolism and the benefits can be observed already after a short period of abstinence from smoking, although it occurs several years before the risks approach those of the never-smoker.

The influence of genetic factors is always more evident in defining the relationship between smoking and cardiovascular events and disease [21-23].

Genetic disorders may be single or complex, multifactorial or polygenic, this means that they are likely associated with the effects of multiple genes in combination with lifestyle and environmental factors. Multifactorial disorders involve primarily heart and blood vessels. Although complex disorders often cluster in families, they do not have a clear-cut pattern of inheritance. This makes it difficult to determine a person's risk of inheriting or passing on these disorders. Complex disorders are also difficult to study and treat because the specific factors that cause most of these disorders have not yet been identified. However, smoking [21-23] seems to play a strong role at different levels.

The review of Armani *et al.* [24] analyzes the current interaction between DNA variants in some genes and cardiovascular diseases as well as the role of smoking exposure.

Tobacco smoking remains the second largest preventable cause of mortality and morbidity worldwide. For what concerns cardiovascular system, exposure to tobacco smoke causes coronary disease, atherosclerosis and ischemic vessel disease.

The degree of this risk is proportional to the amount of smoking and it varies from individual to individual because of individual differences in genetic background.

While the chemical properties of tobacco smoke are relatively well characterized, the mechanisms by which smoking leads to disease and the genetic factors that determine susceptibility to these diseases are not well understood.

The interaction between DNA variants in some important genes, cardiovascular diseases and exposure to cigarette smoke significantly modifies the association between genetic variants and cardiovascular risk with a marked increase of the last parameter.

Genetic disorders are also strongly related to oxidative stress that is a modulator of cardiovascular response [25].

Oxidative stress is a term used to describe the level of structural damages caused by free oxygen radicals in a cell, tissue or organ. Free oxygen radicals are a group of molecules that derive from oxygen metabolism and exist in all aerobic organisms. Usually, endogenous sources originate these compounds. Among exogenous sources, smoking exposure in both its forms, active and passive, plays a significant role, but not the strongest, in inducing free oxygen radical formation [26]. Formation of oxygen radical is the result of oxidative reactions that characterize intracellular respiratory metabolism [27].

Individuals negatively feel the action of these compounds associated with antioxidant depletion being the latter factor that impedes an excessive LDL-Cholesterol oxidation. Children exposed to passive smoking [28] are exposed to oxidative stress at different levels, including atherosclerosis.

The level of oxidative stress is the result of the balance between damaged metabolism and degree of its effective restoration.

Preventive measures against oxidative stress from smoking must face towards, at least, three ways: lifestyle changes consisting particularly of avoiding smoking, playing physical activity and diet supplementation associated with the control of other major cardiovascular risk factors also using drug administration if it is necessary.

Avoiding smoking exposure would be the better way to change the oxidative stress level; about diet supplementation effective results [29-34] may be obtained particularly with Vitamin C and E since their concentrations in smokers were found significantly lower than that of non-smokers. In addition, in a little group of subjects [34] oral supplementation of vitamin E could attenuate transient impairment of endothelial function after heavy smoking exposure as a consequence of an improvement of the oxidative status but not chronic endothelial dysfunction. Therefore, one can conclude that among different antioxidants particularly vitamin C and E are capable to reduce the effects of oxidative stress.

In the review of Grassi *et al.* [35]. some interesting physio-pathological features are discussed. Increasing evidence supports the hypothesis that oxidative stress and endothelial dysfunction are the fundamental mechanisms linking cigarette smoking to cardiovascular disease. The cardiovascular system is a rich source of NADPH oxidase - derived reactive oxygen species, which under pathological conditions play a fundamental role in vascular damage. Endothelium-derived nitric oxide (NO) plays a major role in the regulation of vascular tone, structure, and function and endothelial dysfunction could be considered as the first step in the pathogenesis of atherosclerosis and cardiovascular disease. Indeed, the bioavailability of NO is modulated by reactive oxygen species that degrade NO, uncouple NO synthase, and inhibit synthesis. Reduced bioavailability of NO and consequent endothelial dysfunction are involved in the initiation, progression and complications of atherosclerosis and are also predictive of future cardiovascular events. Thus, although data from clinical trials exploring the role of antioxidants on cardiovascular risk and disease are equivocal as yet, the role of oxidative stress in cardiovascular disease is an important area of research, which is likely to continue to be fruitful.

Conversely, Varela-Carver *et al.* [36] in their review treat the histochemical and structural features of myocardial cells and vascular endothelium as a combined effect of oxidative stress and endothelium. Active and passive exposure to cigarette smoke (CS) increases the risk

of, ischaemic heart disease and has deleterious effects. Exposure to CS increases infarct size in experimental models of coronary occlusion and reperfusion. Among many possible mechanisms of these deleterious effects in intact animals and humans three have more substantial evidence: 1) functional alterations of endothelial cells, neutrophils and platelets; 2) impaired mitochondrial function and energy metabolism caused by toxins in CS, including oxidative free radicals; 3) increased arterial stiffness and vulnerability of the atherosclerotic plaque. In addition to the various pro-mitogenic, carcinogenic and apoptotic pathways are thought to be affected and upregulated by CS, a direct necrotic action on cardiomyocytes is also believed to exist. Many, if not all, of these alterations are caused by oxidative stress, either as a direct consequence of inhalation of free radicals, or by induction from the vast range of chemicals present in both the gas and solid phase of tobacco smoke.

When we face up to a current impact of the relationship between smoking and cardiovascular-related disease endothelial progenitor cells must be discussed since there is evidence that their interference with smoking is always more documented.

Endothelial progenitor cells [37] are primitive cells made in the bone marrow that can enter the bloodstream and, then, reach those blood vessel areas where an injury has produced damage. Therefore, endothelial progenitor cell function is to help repairing damage. Therefore, depletion in their number may contribute to blood vessel disease.

The exact role of these cells in endothelial injury restoration is yet unclear. In the past, the regeneration of an injured endothelium was attributed to migration and regeneration of endothelial progenitor cells. On the contrary, recent studies [38-42] demonstrate that additional factors may contribute actively to injured endothelium regeneration. Therefore, circulating endothelial progenitor cells would have a lower importance than that assigned. Data would indicate that there might be at least two different types of circulating cells that primarily are capable to induce endothelial regeneration, specifically cells coming from bone marrow as well as non-bone marrow cells. The latter could arise from either extra bone-marrow sources, namely stem cells living into different tissues, or vessel wall-derived endothelial cells.

Nicotine and the complex of its metabolites would influence both number and activity of circulating endothelial progenitor cells with augmentation and enhanced functional activity at relatively low concentrations. On the contrary, toxicity would be observed at a higher metabolite concentration [43]. Since nicotine is an active metabolite of smoking, we can deduce that the exposure to environmental tobacco smoke may have adverse effects on endothelial progenitor cells reducing the process of endothelial revascularization and, then, triggering endothelial dysfunction.

An excellent review of Di Stefano *et al.* [44] discusses these features and also analyzes the results of literature.

Accumulating evidence indicates that circulating endothelial progenitor cells (EPCs) derived from bone marrow contribute to re-endothelization of injured vessels as well as neo-vascularization of ischemic lesions in either a direct or an indirect way. Moreover, the number and/or the functional activity of EPCs are inversely correlated with risk factors for cardiovascular disease. Among different risk factors, cigarette smoking is a major cause of reducing the number and functions of circulating EPCs and that can be identified by *in vitro* and *in vivo* models.

The relationship between smoking and inflammation that triggers a lot of mechanisms leading to atherosclerosis, needs some comments because inflammatory phenomena are one of the most important steps linked to all factors already discussed, primarily endothelial activation. Soluble mediators, leucocytes, endothelial cells and smooth muscle cells interact [45-47] to begin the inflammation of tissues at different levels, including vascular wall.

Enzymes, enzymatic chains and biochemical metabolites play a well defined role but white blood cells seem to be a strong factor, through their recruitment, of maintaining and progressing lesion.

The review of Pistoia *et al.* [48] analyzes the relationship between cyclooxygenase and atherosclerosis as modulators of plaque instability in the presence of cigarette smoking.

Chronic smoking is associated with functional and structural vascular changes underlying inflammatory processes responsible for plaque formation and rupture. Cyclooxygenase (COX) is the key enzyme linking smoking action to inflammatory damages: it is responsible for the conversion of arachidonic acid to prostanoids, and lipid mediators involved in most of pathological processes. Two COX isoenzymes have been characterized, COX-1 and COX-2, that differ in terms of regulatory mechanisms of expression, tissue distribution, substrate specificity, and preferential coupling to upstream and downstream enzymes. The pathogenetic role of chronic smoking in vasomotor dysfunction, inflammation, and modification of lipids underlying the initiation and the progression of atherosclerosis as well as remarking the hypothesis that plaque composition rather than plaque size is the real determinant of the plaque evolution toward rupture and the major cause for acute ischemic syndromes are discussed. The concomitantly higher expression of EP4, COX-2, mPGES-1, MMP-2 and MMP-9 in unstable plaques is focused and the role of PGE₂ as pathophysiological link between smoking, COX-2 and MMP activity is stressed.

Genetic defects, which are strongly influenced adversely by cigarette smoking as already described, play a significant role in all cardiovascular disorders, primarily congenital heart defects.

Malformations of the heart and blood vessels account for a large number of birth defects in humans occurring for about 1% of all live births [49,50]. Their appearance involves in a large number of observation factors linked to the inheritance or family history, although external events may induce cardiovascular defects at the birth and, among these, undoubtedly smoking habit [51]. In addition, some types of congenital heart defects would seem related to smoking with a major incidence when compared to other congenital heart defects.

Maternal smoking and tobacco exposure during pregnancy seem to be associated with an increased risk of congenital heart disease [52], especially septal and right-sided obstructive defects.

The review of Gianicolo *et al.* [53], with regards to the aforesaid consideration, further underlines that cigarette smoking is a powerful human germ cell mutagen and teratogen. Congenital heart defects (CHD) are the most prevalent of all birth defects and leading cause of death in the first year of life. In addition, the epidemiology of the impact of cigarette smoking on CHD risk as well as the potential biological mechanisms of smoking-mediated abnormal cardiac development is discussed. Although epidemiological studies of association between parental smoking and CHD are limited, biological evidence support the concept that cigarette smoking may substantially contribute to the etiology of CHD through induction of either male and female germ-cell mutation or interference with epigenetic pathways. However, further research is needed to better define the relationship between parental smoking and the risk of heart defects as well as to assess parental-fetal gene-smoking interactions.

Discussed data permit to assess the complex relationship existing between smoking and smoking-related risk factors capable to influence or induce cardiovascular events as well as the genetic, epidemiological, biochemical and pathological associated features.

Indeed, a question arises analyzing these concepts: Can we identify certainly smoking-related cardiovascular disease?

The review of Santarelli *et al.* [54] sets to clarify such subject.

The article discusses on the current techniques employed to assess endothelial dysfunction in different categories of smokers. Simple but effective method to assess regional and local properties of large arteries for epidemiologic studies is, in particular, high resolution magnetic resonance to quantify, in a single examination, vascular function at different sites of peripheral and central arteries. Finally, the role of positron emission tomography and magnetic resonance flow mapping is described to assess myocardial microcirculation at rest and under external stressors.

Finally, some concepts should be emphasized to estimate the significance of smoking cessation that is the goal to reach for avoiding the risk from cigarette smoking.

Since there is evidence [1-5] of harmful effects that smoking is able to exert on several tissues and organs of our body, an always greater amount of current smokers become past-smokers particularly when they suffered from an ischemic heart attack. Therefore, the number of past-smokers is continuously increasing.

Benefits of smoking cessation and better techniques to reach this goal have been estimated differently in various findings [55-64].

Strong motivation to stop smoking may derive from the knowledge of harmful effects of smoking particularly for those individuals who become frightened following health problems and are persuaded that positive outcomes may occur avoiding smoking.

Nicotine dependence, on the contrary, may require, sometimes, a specific treatment.

After an ischemic event, particularly acute myocardial infarction, risk associated with smoking, in presence of smoking cessation, declines rapidly [63], although some concepts must be kept in mind. The decline reaches maximum degree within the first three years following smoking cessation, and coronary risk due to cigarette smoking halves its harmful effects on cardiovascular system. Conversely, a further decline in cardiovascular risk occurs slowly after this time period so that the total cessation of the risk needs from five to fifteen years depending on the number of smoked cigarettes and previous duration of smoking habit.

In the Parisian Prospective Study [64], among a cohort of 7,746 men with an age from 45 years to 54 years at the beginning of the enrolment into the study protocol, there was evidence, after twenty year follow-up, that a daily consumption of 11 cigarettes increased the incidence of ischemic heart disease by 40 percent, and stopping smoking could reduce this observed incidence of more than a quarter. However, large-scale studies on smoking cessation are yet a limited number and, therefore, do not permit certain conclusions.

Differences of time in disappearing coronary risk after smoking cessation could be related also to the presence or not of associated coronary risk factors, and, often, the role of the other risk factors continue to maintain in the time those coronary changes that stopping smoking would have, probably, reduced in severity and extension.

Globally, cigarette smoking consumption has undergone a reduction although through cyclic phases of increased/decreased/ and again increased smoking habit [3].

The review of Gaemperli *et al.* [65] treats the relationship between nicotine addiction and coronary artery disease through an analysis of the type of damage caused by smoking on cardiovascular system. The main results obtained by smoking cessation also by pharmacological therapy are estimated and focused in relation to the possible coronary lesion.

In smokers, the cessation of smoking is the most important intervention for cardiovascular risk reduction. Total mortality can be reduced by 36% which is comparable to established modern secondary preventive therapies. Nonetheless, non-aided cessation attempts are notoriously poor with a success rate of less than 10%. Patient counselling and pharmacological therapies are important aids for smoking cessation and can improve success rates by two to threefold. However, there is still need for improved strategies of smoking cessation to reduce the high socioeconomic impact of smoking.

Taken together, the articles in this issue provide a current approach to a better understanding the role of cigarette smoking as a risk factor of cardiovascular disease revising all those concepts of absolute certainty on the subject as well as the newer observations of how cardiovascular risk may be increased as an effect of smoking compounds or reduced by techniques of smoking cessation. Therefore, this issue further contributes to update researchers, physicians and also students on a subject that is continuously expanding.

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Executive Editor

Aurelio Leone, M.D., Fellow of the Royal Society for Promotion of Health, London, UK

Co-Executive Editors

Luigi Landini and Eugenio Picano, CNR Institute of Clinical Physiology, Pisa, Italy

Dr. Aurelio Leone

Via Provinciale 27
19030 Castelnuovo Magra (SP)
Italy
Tel/Fax: +390187676346
E-mail: reliol@libero.it