Passive Smoking, Endothelial Dysfunction and Related Markers in Healthy Individuals: An Update[#]

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Abstract: By the analysis of previous studies, functional and biochemical markers related to environmental tobacco smoke (ETS) exposure are discussed. 18 healthy never smokers, 12 men (67%) and 6 women (33%) aged from 21 to 55 years (mean: 34+/-9 ys.) underwent experimental procedures twice. in a smoking free environment and in the same environment polluted by 35 ppm carbon monoxide derived from smoked cigarettes.

Brachial artery ultrasonography, exercise stress testing, heart rate (HR) and blood pressure (BP) monitoring, and carboxyhaemoglobin (COHb) concentrations were examined.

Five markers related to ETS exposure of healthy individuals could be demonstrated: l. Impaired FMD as an effect of endothelial dysfunction, 2. Transient increase in systolic BP; 3. HR increase; 4. Diminished tolerance to exercise; 5. Increased COHb blood concentrations. Some of these feel the effects of sympathetic stimulation induced by both nicotine and carbon monoxide.

Since both active and passive smoking are believed to be a chemical toxicosis, avoiding ETS exposure of healthy non-smokers must be a categorical imperative.

Keywords: Passive smoking, healthy individuals, endothelial function, exercise tolerance, heart rate, blood pressure, carboxyhaemoglobin.

INTRODUCTION

It's almost totally accepted opinion that the subjects exposed to passive smoking have severe alterations of both acute and chronic type affecting heart and blood vessels.

A lot of papers [1-18] have documented functional or structural cardiovascular changes following exposure to passive smoking either clinically or experimentally. They experienced different mechanisms whatever approach had been studied – and there were several approaches of study: clinical, biological, metabolic, epidemiologic, statistic, and other which, specifically, identify different pathogenetic mechanisms of damage – leading to only one result which is a reversibly functional harm of the heart and blood vessels following acute exposure, and morphological alterations that become, in the long run, irreversible lesions after chronic exposure [1-8]. Therefore, the American Heart Association has included passive smoking among the major risk factors for heart disease in both adults and children [4].

No country is free from the damage caused by passive smoking exposure, which plagues developing and developed countries alike, although with different results due to different lifestyles and diffusion of antismoking campaigns. Passive smoking influences negatively the health of both adults and children particularly following chronic exposure.

The purpose of this review is to update a previous paper [19] that analysed in detail the functional and biochemical markers able to assess cardiovascular exposure to environmental tobacco smoke (ETS) as well as type of accompanying alterations in never smoker healthy individuals through the discussion of our previous studies.

ANALYSIS AND COMMENTS OF PREVIOUS STUDIES

Study population consisted of eighteen healthy individuals (Table **1**), 12 males (67%) and six females (33%) aged from 21 years to 55 years with a mean age of 34+/-9 years.

Table 1. Characteristics of Study Population

Total number	18 (100%)
Males	12 (67%)
Females	6 (33%)
Mean age+/-SD (years)	34+/-9
Previous medical history	
Yes	0
No	18

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Subjects underwent study protocol twice. The experimental procedures were conducted by using exercise stress testing on a bicycle ergometer, brachial ultrasonography, heart rate (HR) and blood pressure (BP) monitoring, and carboxyhaemoglobin (COHb) dosage in blood samples (Table **2**).

Table 2. Experimental Tests Used in Study Population

1. Exercise stress testing on a bicycle ergometer
2. Brachial artery ultrasonography
3. HR monitoring
4. BP monitoring
5. COHb determination in venous blood samples

On a first time, individuals were in a smoke-free environment and, then, again in the same environment polluted by carbon monoxide at a concentration of 35 ppm obtained by a method of cigarette combustion described elsewhere [17]. In our opinion, these experimental tests could provide useful parameters to identify the effects of ETS on cardiovascular system following an acute exposure.

In the experiment, exercise stress testing in healthy individuals [17] measured the peak of exercise (watt) and time to recovery baseline HR (TRBHR, minute) in 60 cubic metres of enclosed space not polluted by cigarette smoke and, then, in the polluted same environment. After exercise conducted in the smoke-environment, a statistically significant increase (P< .01) in mean TRBHR, which passed from a mean time of 8.5+/-5 minutes to a mean time of 19.04+/-4 minutes after exposure, was documented. In addition, two-hour ambulatory monitoring following ETS exposure displayed mean HR 89+/-4 beats per minute versus 77+/-4 beats per minute measured in the smoke-free environment. Mean systolic BP was 134+/-17 mmHg after exposure versus 124+/-21 mmHg (P<.01) while diastolic BP displayed mean values of 79+/-4 mmHg in smoke-environment versus 76+/-5 mmHg in the smoke-free environment (P>0.05, statistically not significant).

By brachial ultrasonography, flow-mediated dilation (FMD) was the most meaning examined parameter since it is a benchmark of the endothelial function. FMD was firstly measured in an environment polluted by ETS during 30-minute stay of studied subjects. During exposure [18], mean FMD was 6.8+/-7.8% versus pre-exposure measures of 12.6+/-7.8%, a statistically significant difference (P<.01). On the contrary, no change existed for endothelium-independent vasodilation induced by nitroglycerin (GNT-vasodilation) which is a parameter not depending on endothelial function, when individuals exposed to ETS were compared with themselves not exposed. Sublingual nitroglycerin at a dose of 400 μg was administered and response to the drug estimated three to four minutes later at the maximum of dilation either in smoke or in smoke-free environment. Mean GNT-vasodilation was 281+/-51 ml/min in the smoke environment and 279+/-51 ml/min in the smoke-free environment with a non-statistically significant difference (P> .05).

These data suggest that endothelial dysfunction of healthy individuals was related to a FMD impairment during acute smoking exposure although with transient effects.

COHb, determined in venous samples before and after ETS exposure, increased significantly (P<.01) in the smoking environment, starting from a mean value of 0.8+/-0.4% to a mean concentration of 1.7+/-0.4%, reaching in some individuals increased concentration up to 4 times.

Table **3** reports the main changes observed for the examined parameters before and during smoking exposure as well as their statistical significance.

The analysis of these results permitted to identify five markers of cardiovascular impairment related to ETS exposure: 1. Diminished tolerance to exercise; 2. Endothelial dysfunction; 3. Increase in systolic BP; 4. Increase in HR; 5. Increased COHb concentrations.

These markers, which follow transiently acute exposure to passive smoking, may be easily deduced by a direct observation deriving by comparative pre and post-smoking measures. However, there would be also current evidence that the role of autonomic stimulation can be determined by an indirect analysis of studied parameters.

Therefore, the assessment of these markers strongly identifies non-smoker healthy individuals who are exposed to ETS. In addition, there is always more convincing evidence that each marker plays a different role and importance to influencing cardiovascular responses associated with smoking exposure as a large series of reports, analysed, in detail, in my previous paper [19] and further discussed by this updating, seem show [19-64].

ENDOTHELIAL DYSFUNCTION

There is now acquired evidence that the endothelium plays a pilot role in the maintenance of vascular tone through the action of different chemical mediators, which act respectively as vasodilator and and vasoconstrictor agents that, in endothelium intact, balance their responses providing the normality of endothelial function [20-22, 65-68].

Endothelial function is the most important parameter adversely changed during exposure of an individual to ETS [13].

Endothelium is a cellular monolayer that lines the entire vascular bed at the interface between both plasma and cellular blood and the vessel wall. Endothelial cells are contiguous elements linked among themselves by inter-digitations that contribute to form a continuous structure capable of influencing and interacting both blood surface and endothelial layer. By this shape, endothelium is intimately linked to control vasomotor tone and preventing athero-sclerotic plaque formation [19].

Table 3. Main Parameters Examined before and During Smoking Exposure

Parameter Assessed	Smoking Exposure	No Exposure	P Value
1. Exercise stress testing			
TRBHR (mean)	19.04+/-4 min	8.5+/-5 min	<0.01
2. Brachial Ultrasonography			
FMD (mean)	12.6+/-7.8%	6.8+/-7.8%	<0.01
GNT-dilation (mean)	281+/-51 ml/min	279+/-51 ml/min	NS
3. HR monitoring			
HR (mean)	89+/-4 beats/min	79+/-4 beats/min	< 0.05
4. BP monitoring			
Systolic BP	134+/-17 mmHg	124+/-21 mmHg	< 0.01
Diastolic BP	79+/-4 mmHg	76+/-5 mmHg	NS
5. COHb venous samples			
COHb (mean)	1.7+/-0.4%	0.8+/-0.4%	<0.01

As mentioned, endothelium produces several relaxing factors including, mainly, nitric oxide (NO) [21], prostacyclin and a not yet completely defined hyper-polarizing relaxing factor (EDHF). About the produced contracting factors, cyclooxygenase-dependent contracting factors and endothelin-1 have a primary role in inducing vasoconstriction.

Altered endothelium as a consequence of harmful stimuli including exposure to ETS triggers all those mechanisms that lead to atherosclerosis [23, 24]. In addition, endothelial dysfunction has a strong association with essential hypertension [25, 26].

Exposure to ETS has been identified as a strong factor of endothelial dysfunction either after acute or chronic exposure. There is clear evidence now [69] that this concept needs of updating. Endothelial dysfunction following acute exposure is usually transient and, therefore, unable to cause stably morphological alteration. However, it triggers mechanisms of structural damage of cardiovascular system when it occurs repeatedly and irregularly reaching levels of exposure which characterize chronic damage. Endothelial activation, induced also by acute and frequent exposure, seems to be the main key triggering atherosclerotic process [70].

Several smoking compounds influence adversely the function of endothelial cells. They can induce endothelial dysfunction of different type and degree, sometimes earlier than that due to other major cardiovascular risk factors like hypertension or increased LDL-Cholesterol which, usually, needs a chronic damaging activity. On the contrary, functional disorders of endothelium due to ETS are as early as smoking exposure starts as several studies undoubtedly show [16, 18, 27-30].

Among the smoking compounds, primarily nicotine, contained into both fresh tobacco leaf and burned tobacco, and carbon monoxide, produced only during cigarette burning, cause changes in endothelial function [27]. Observations seem to show that the effects of smoking compounds damaging cardiovascular system are continuously updating and identifying an active metabolic role particularly of nicotine in every phase of cardiovascular damage [71].

Carbon monoxide induces a large number of alterations including endothelial dysfunction which recognizes either a functional mechanism or later structural changes related to atherosclerosis development [28, 31, 32]. Quantitatively, these alterations are the most severe changes caused by smoking compounds [67].

Findings conducted by Celermajer *et al.* [29] compared endothelial function of the artery vessels in three different groups of healthy individuals. The first group enrolled active smokers, the second group lifelong non-smokers who, however, were exposed to ETS, and, finally, the third group consisted of healthy individuals who were exposed inconstantly and irregularly to passive smoking. Endothelial function was assessed by using brachial ultrasonography that measured vascular reactivity of brachial artery. Obtained results documented that either active or passive smokers had significantly impaired endothelial function, although of different degree, because of reduced NO production and release.

As endothelial dysfunction is considered to be an early event in the pathogenesis of the atherosclerotic plaque, studies have been conducted in both humans and animals to clarify the role of ETS exposure. Apart from the findings of Giannini *et al.* and Celermajer *et al.* [18, 29], there is

evidence that reduced aortic elasticity in men, part of whom affected by ischaemic heart disease, characterized ETS exposure as Stefanidis *et al*. [33] experimentally documented. Experimentally, animals like cockerels and rabbits exposed to ETS impaired heavily endothelial function and accelerated atherosclerosis progression [34-36]. Therefore, it would be very suitable to carry out all those preventive measures which may reduce endothelial dysfunction in individuals involuntarily exposed to ETS [6]. Among those measures which can fight endothelial dysfunction, there are some linked to individuals' lifestyle such as physical activity and antioxidant dietary supplementation with vitamin C and E, folates, fish oil or moderate consumption of red wine, some addressed to reduce the incidence and adverse effects of major coronary risk factors, and, finally, some others that require specifically a therapeutic approach when non-pharmacological prevention is unable to obtain the settled result. In any case, endothelial dysfunction should be considered an independent prognostic marker for cardiovascular disease and also associated with coronary pathology [30].

In conclusion, the analysis of mentioned observations undoubtedly shows that ETS exposure triggers early and constantly endothelial dysfunction either in those individuals who suffer from a cardiovascular disease or, also, in healthy subjects. Always newer updates [65-71] contribute to increase the significantly adverse effects of ETS exposure on endothelial function. In addition, when there is endothelial dysfunction associated with other markers related to ETS exposure no doubt that a healthy individual has been exposed to passive smoking.

INCREASED SYSTOLIC BP

Systolic BP is a clinical parameter of easy determination and often linked to endothelial dysfunction particularly in those individuals who display or will display late essential hypertension [19, 25, 26, 68].

The acute response of BP to ETS exposure seemed to cause an increase in systolic values in some reports [37, 38], whereas others [39] did not reach the same conclusions. However, current opinion [72, 73] supports increased systolic BP either after acute or chronic exposure, although with different characteristics and mechanisms of onset [74].

The course of BP as an effect of smoking exposure needs some explanations. Initially, a vasoconstriction mechanism mediated by nicotine causes acute, but transient increase in systolic BP maintained by autonomic nervous system stimulation [74] as it will be described in more detail later. This phase is followed by a decrease in BP as a consequence of depressant effects played chronically by nicotine itself. Simultaneously, carbon monoxide acts directly on arterial wall causing, in the long run, structurally irreversible alterations. At this time, it will be observed a slight change in systolic BP that will enhance, often stably [40]. This result is a typical picture of prolonged and chronic exposure to ETS. On the contrary, acute exposure to ETS recognizes a transient increase in systolic BP due to a multiple mechanism that involves both nicotine and carbon monoxide: endothelial dysfunction, adrenal and sympathetic stimulation and increased COHb concentration [41-44]. Increased systolic BP after acute exposure to ETS was also found by Mahmud and Feely [45], whereas Leone and Corsini [46] documented a decrease in systolic BP but following repeated and irregular acute exposure to ETS. In addition, decrease in BP was proportional to the increased COHb concentrations. However, Leone and Bellotto demonstrated increased systolic BP after isolated acute ETS exposure of individuals [74].

These observations support the hypothesis that different responses characterize BP according to the fact that this parameter is assessed immediately after acute exposure or after repeated and chronic exposure. Acute exposure is followed by a transiently significant increase in systolic BP, whereas chronic exposure is, usually, followed by reduced or increased systolic BP depending on the presence of reversible or irreversible alterations in arterial wall caused mainly by carbon monoxide.

In addition to impaired blood vessel dilation, acute exposure to ETS influences arterial stiffness and, consequently, increases BP [35, 45, 47, 48, 69]. This changes on arterial stiffness and consequently changes in BP usually occur before they are clinically manifest [16], involve not only carotid but also aortic and coronary artery function [33] and are greater than those seen when a non-smoker smokes a single cigarette.

Usually, in healthy individuals arterial stiffness is a developing event related to age and atherosclerosis. In addition, there is evidence that increased arterial stiffness is associated with a major incidence of both non-fatal and fatal cardiovascular events. Indeed, the assessment of arterial stiffness is increasingly used in the clinical assessment of patients [75, 76]. Morphologically, the arterial stiffness is caused by progressive degeneration and fragmentation of elastic matrix of the arterial wall with connective proliferation. In addition, the elastic properties of conduit arteries vary along the arterial tree with more elastic proximal arteries and stiffer distal arteries. This heterogeneity is caused by the molecular, cellular, and histological structure of the arterial wall, which differs between the various parts of the arterial tree [76, 77]. Arterial stiffness is associated with vascular dysfunction in healthy individuals with vitamin D changes [78]. From these observations, there is evidence of a strong relationship between vascular dysfunction, arterial stiffness and atherosclerosis, all together events induced by passive smoking exposure [79]. Therefore, changes in arterial stiffness cannot be only considered as a marker of vascular aging since they feel the action of different mechanical and chemical stimuli.

Coronary artery stiffness, which feels the effects of ETS exposure more heavily than carotid and cerebral arteries [80], is influenced also by other major cardiovascular risk factors like diabetes mellitus and oxidative stress [81]. In addition, results [82-85] demonstrated that large coronary vessels responded passively to changes in distending

pressure as well as in cross-sectional area following a different number of pharmacological and chemical stimuli including ETS exposure. Large epicardial coronary arteries are, usually, primarily involved in stiffness changes although the same changes have been well identified in small coronary arteries [79]. Exposure to ETS favours arterial stiffness increase that, therefore, may be identified as a strong risk factor for ischaemic heart disease.

In conclusion, even if assessing systolic BP immediately after ETS exposure may be difficult unless in experimental findings, one cannot deny its increase and consequently, its interpretation as a marker of acute ETS exposure.

INCREASED HR

It is well established that acute exposure to ETS modifies HR [16].

HR increases probably as an effect of adrenal and sympathetic stimulation [43, 49, 50, 74], even if a greater meaning in assessing ETS exposure would have reduced HR variability [51] more than the simple increase in HR.

HR variability is a parameter that can be measured on the electrocardiogram by assessing variation in R-R intervals. Therefore, its establishing may be more difficult than that of measuring beats/min of HR. Impaired HR variability may be associated with triggering of malignant arrhythmias and sudden cardiac death [16, 52]. In addition, Barnoya and Glantz [16] underlined that two hour exposure to passive smoking was associated with a 12% reduction in HR variability and the reduction could be associated with an increased risk of ventricular fibrillation or ventricular tachycardia particularly in individuals suffering from an ischaemic heart disease. Restoration of baseline HR variability was documented only two hours after ETS exposure. Evidence indicates that in the period before an ischaemic ventricular fibrillation, R-R variability associated with ST elevation in patients with acute myocardial infarction may be seen [86].

A simple record of HR is an easy procedure during ETS exposure to assess its changes: In addition, the mechanism that triggers malignant ventricular arrhythmias is undoubtedly sympathetic stimulation [53] that tends to dry up in time.

Interaction between passive smoking compounds, increased catecholamine release and sympathetic stimulation are the main pathogenic factors that maintain transiently increased HR following ETS exposure, although the duration in time of HR change occurs shortly [74].

DIMINISHED TOLERANCE TO EXERCISE

The results displayed analysing this parameter following ETS exposure have not received significant updates with regard to what observed in the past since then, as they showed definite answers on the cardiovascular damage.

Exercise stress testing either performed on a bicycle ergometer or treadmill shows a diminished tolerance in healthy individuals as well as in individuals suffering from an ischaemic heart disease in passive smoking environment, although the type and degree of the impairment vary widely [17, 54, 55, 87]. Leone *et al.* [17] studied exercise tolerance of healthy individuals during acute exposure to ETS. Subjects impaired exercise performance in an environment polluted by cigarette smoking and increased significantly COHb concentrations. A significantly prolonged TRBHR was documented in healthy people after exercise. The same individuals showed no alteration of cardiovascular parameters during exercise performed in the same environment not polluted by cigarette smoking. The same experiment was conducted in individuals with pre-existing myocardial infarction who displayed severe alterations in a smoke environment with markedly reduced exercise tolerance and ventricular arrhythmias in a large number of cases [17-87].

McMurray *et al.* [54] studied exercise performance of 8 healthy young women who were 4 smokers and 4 non-smokers. A reduction in exercise duration in passive smoking environment associated with diminished maximal oxygen uptake was identified.

Finally, Pimm *et al.* [55] analysed twice the response to exercise of 20 healthy young men and women: in an environment polluted by carbon monoxide to a concentration of 24 ppm and in an environment not polluted by cigarette smoking. Individuals performed exercise on a bicycle ergometer for 7 minutes. In a smoking environment, a significant increase in COHb concentration which was associated with no other change in cardiovascular parameters was documented. Although no reduced tolerance to exercise was assessed by this study, there is evidence, however, that a slow carbon monoxide concentration in the environment associated with limited exercise duration could have, probably, impeded the appearance of diminished tolerance.

Although with different responses, exercise tolerance in healthy individuals was almost unequivocally reduced during exercise stress testing in passive smoking when compared to that conducted in a smoke-free environment.

When one analyses the exercise tolerance in individuals suffering from ischaemic heart disease, as just mentioned, the response changes most dramatically. Aronow [8] studied the effects of exercise stress testing in 10 men with stable effort angina. The men were exposed to ETS twice: in a well-ventilated room, and in a room where ventilation was absent. Exposure to ETS induced HR, BP and COHb increase which were associated with a statistically significant decrease in angina threshold equal to 22% during exercise, as a result of diminished exercise tolerance. Leone *et al.* [17], and Leone [56] observed markedly reduced exercise tolerance in individuals with pre-existing myocardial infarction as well as life-threatening ventricular arrhythmias during exercise stress testing on a bicycle ergometer performed in a smoking environment compared to that conducted by the same individual and in the same environment not polluted by carbon monoxide. Finally,

Allred *et al.* [57], and Sheps *et al.* [58] documented the appearance of myocardial ischaemia and ventricular arrhythmias in individuals with a history of coronary artery disease when they performed exercise in an environment polluted by carbon monoxide.

Different cardiovascular parameters have been assessed in the examined studies related to ETS exposure. Table **4** summarizes the main of them measured in healthy individuals.

Table 4. Parameters of Exercise Stress Testing Assessed During ETS Exposure in Healthy Subjects

Studied Parameter	Response	Main References
HR	Increased	Barnoya and Glantz [16] Pope *et al.* [51] Leone [53] Leone and Bellotto [74]
BP (systolic)	Increased	Mahmud and Feely [45] Leone and Bellotto [74]
Exercise duration	Diminished	Leone *et al.* [17] McMurray *et al.* [54] Pimm *et al*. [55]
Restoration baseline parameters	Increased	Leone *et al.* [17]
COHb concentration	Increased	Leone *et al.* [17] Marius-Nunez [62] Thomsen and Kjeldsen [63] Kjeldsen *et al.* [64]

These observations display that exercise stress testing is a useful method to assess the adverse effects of ETS exposure on cardiovascular system in both healthy subjects and subjects suffering from an ischaemic heart disease. Therefore, diminished exercise tolerance must be interpreted as an effective marker and a test [88] of acute smoking exposure.

INCREASED COHb CONCENTRATION

Biological monitoring of ETS exposure may be desumed by COHb concentrations of the blood. This parameter strongly related to carbon monoxide inhalation. However, establishing ETS exposure by this parameter may often fail since COHb concentrations derive from either smoking or carbon monoxide produced by chemical industries and car fuel that pollute heavily the environment. However, there is evidence that experimental findings permit to dose COHb levels reached following ETS exposure [17]. COHb concentrations may simply be determined on a venous or arterial blood sample using spectrophotometric methods [59-61].

COHb from smoking depends only on carbon monoxide of burned cigarettes since the other toxic of tobacco smoke including nicotine act in both burned cigarette and fresh tobacco leaf. Such a fact, even if could be considered as a limiting factor for the assessment of harmful effects due to smoking , on the contrary, contributes to clarify specifically some characteristics of ETS exposure. Indeed, carbon monoxide, either clinically or experimentally, affects not only blood haemoglobin but also other structures of blood and body organs [2, 62-64].

Carbon monoxide from ETS exposure determines COHb concentrations into the blood up to four times higher for non-smokers exposed than those seen in similar individuals not exposed to ETS [17]. Indeed, the bond between carbon monoxide and haemoglobin has been biochemically estimated to be two hundred times stronger than that of oxygen and haemoglobin. Therefore, carbon monoxide can reduce oxyhaemoglobin concentrations rapidly and very easily causing clear and early increased concentrations of COHb that can be dosed as a useful marker of ETS exposure in non-smoker individuals. In addition, current evidence indicates carbon monoxide as the strongest tobacco smoking compounds damaging cardiovascular system [66-68].

AUTONOMIC STIMULATION DURING ETS EXPOSURE

The role of the autonomic nervous system stimulation during or following acute exposure of healthy subjects to passive smoking is considered not as a marker of exposure, but rather, a factor responsible and modulator for at least 3 markers of those already described: the endothelial dysfunction, increased HR and increased systolic BP. Lower, or almost absent, is the effect on exercise tolerance and blood concentrations of carboxyhaemoglobin, which seem to depend on the amount of carbon monoxide present in the environment.

Leone and Bellotto [74] demonstrated experimentally the role of autonomic system in HR and ambulatory BP monitoring in passive smoking at 22nd Annual Scientific Meeting-American Society of Hypertension 2007. Authors measured HR and both systolic and diastolic BP in non-smoking exposed healthy volunteers. BP was recorded using ambulatory BP monitoring. The study was based on the hypothesis that acute exposure to passive smoking could exert sympathetic effects and, therefore, HR and BP should have had an increase after ETS exposure. In addition, the duration of sympathetic stimulation was recorded. Significantly increased HR and systolic, but not diastolic, BP reached the top 75 minute after smoking exposure to fall at the baseline levels within two hours. Based on these results, authors concluded that autonomic stimulation during and after acute exposure to ETS occurred late and finished quickly, although it could be transiently identified in exposed healthy subjects. Several factors adversely influence the response of autonomic system which also feels the effects of aging during both acute and chronic ETS exposure [89]. There is convincing evidence that passive smoking

stimulates sympathetic nervous system inhibiting also vagal activity with consequences on heart and blood vessel function as a result of both nicotine and carbon monoxide effects [14, 90-93]. Sympathetic alterations may be linked to increased mortality rate particularly in patients suffering from chronic heart failure [94]. However, controversies still exist on the effective role of ETS exposure on HR and BP [90], although their increase cannot be denied in active smokers. Probably, environmental smoking compound level influence both autonomic stimulation and result of it.

Based on these observations, it is clear, however, that stimulation of the autonomic nervous system during exposure to ETS should be seen as a major modulator of the effects and not a marker of exposure to secondhand smoke easily documented.

CURRENT & FUTURE DEVELOPMENTS

The expected progresses in control of ETS exposure of non-smokers individuals are still far to be obtained. Therefore, identifying certain markers easily related to exposure might help to solve this unsolved problem.

It can however identify, according to the results of findings conducted until now on the subject, some markers that allow diagnosing exposure to secondhand smoke. Two of these markers, HR and systolic BP, are easy and immediate detection. The remaining 3 markers, assessment of endothelial function, exercise tolerance and COHb concentration, even if of simply establishing, require diagnostic procedures such as the brachial ultrasonography, exercise stress testing on a treadmill or bicycle ergometer, and the dosage of blood concentration of carboxyhaemoglobin.

Whether they are individually or together considered, the markers that show exposure to secondhand smoke are, if chronic and prolonged exposure, the same cardiovascular risk factors that increase the incidence of major cardio-vascular events in smokers and nonsmokers. Therefore, the presence of these markers, which allow identifying individuals exposed to passive smoking, should be carefully considered. Among these, particularly changes in endothelial function that are the door to atherosclerosis, and may coexist with essential hypertension, have to be attentively inter-preted. In addition, a correct endothelial function has been identified as a new therapeutic target area [95] to control the rate of cardiovascular events.

Thus, from these considerations, there is a strict liability "make", in spite of themselves, cardiovascular risk factors in people, who may be free, as a result of exposure to secondhand smoke. It is absolutely urgent need to avoid, in particular for non-smoking individuals, any contact with tobacco smoke.

The way for the future must be to fight secondhand smoke exposure of nonsmokers not taking refuge behind the pretext that there are still doubts on the determinism of the damage. The scientific literature shows that more than 90% of the works demonstrates the power of passive smoking to determine cardiovascular damage especially in certain age groups such as children [96]. There is clear evidence that children exposed to secondhand smoke at home are at higher risk of respiratory problems and, in later life, cardiovascular. It is to be hoped, therefore, a joint effort to achieve the goal of creating a society free of smoking. This requires the future.

CONCLUSION

Exposure to ETS is a strong risk for individual's health so that the American Heart Association has included passive smoking among the major risk factors for heart disease in both adults and children [4]. Therefore, establishing diagnostic markers that permit to identify carefully ETS exposure, particularly for non-smoker healthy individuals, plays a crucial role in preventing the damage caused by exposure.

Current evidence still underlines that five markers, as seen in the past [19], can be correctly associated with ETS exposure. All of them can be related to biochemical and physiopathological changes that induce endothelial damage and, consequently, atherosclerotic plaque formation, stable hypertension and autonomic nervous system stimulation.

Each marker can determine stronger effects on a vascular or biochemical structure of cardiovascular system rather than another, but, however, all lead to a damage of the heart and blood vessels in healthy individuals either adults or children when they are exposed chronically or acutely and repeatedly to ETS.

Since these markers are closely related to smoking toxics, the simplest way to reach effective results in their prevention is to prohibit smoke particularly in schools, workplaces and public buildings by environmental policy interventions that may have a greater impact when carried out over multiple setting [97, 98].

Such behaviour could be followed by a decrease in cardiovascular risk primarily for those individuals suffering from an ischaemic heart disease or other form of vascular disease, but also for some special categories of subjects like children living with smoking parents. In my opinion, while respecting the rights and individual freedom, interventions to prevent and control smoking habits also should be conducted in private homes to further reduce cardiovascular risk from passive smoking. Indeed, smoking has been defined as a chemical toxicosis [99] which is able to cause detrimental effects either of acute or chronic type on different structures of the body being some of these like cardiovascular system target organ.

CONFLICT OF INTEREST

No conflict of interest.

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