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Review

Secondhand smoke as an acute threat for the cardiovascular system: a change in paradigm

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The evidence that active smoking is a risk factor for cardiovascular disease (CVD) and the leading cause of preventable death is overwhelming. However, numerous epidemiological findings indicate that even passive exposure to cigarette smoke may exert detrimental effects on vascular homoeostasis. Recent experimental data provide a deeper insight into the pathophysiological mechanisms linking secondhand smoke (SHS) to CVD. Importantly, most of these effects appear to be characterized by a rapid onset. For example, the relatively low doses of toxins inhaled by passive smoking are sufficient to elicit acute endothelial dysfunction, and these effects may be related, at least in part, to the inactivation of nitric oxide. Moreover, passive smoking may directly impair the viability of endothelial cells and reduce the number and functional activity of circulating endothelial progenitor cells. In addition, platelets of non-smokers appear to be susceptible to pro-aggregatory changes with every passive smoke exposure. Overall, SHS induces oxidative stress and promotes vascular inflammation. Apart from vasoconstriction and thrombus formation, however, the myocardial oxygen balance is further impaired by SHS-induced adrenergic stimulation and autonomic dysfunction. These data strongly suggest that passive smoking is capable of precipitating acute manifestations of CVD (atherothrombosis) and may also have a negative impact on the outcome of patients who suffer acute coronary syndromes.

Increasing awareness of the problem

Epidemiological evidence has unequivocally confirmed that active smoking is a risk factor for cardiovascular disease (CVD) and the leading cause of preventable death.[1,2] For example, the risk of death from coronary heart disease is elevated at least two-fold among smokers when compared with non-smokers,[3,4] two-thirds of sudden cardiac deaths due to acute coronary thrombosis occur in cigarette smokers,[5] and smoking is associated with an ~50% increase in the risk of stroke.[6,7] Clinical and experimental researches carried out over the past years have revealed a number of potential pathomechanisms underlying the increased cardiovascular risk in active smokers. Importantly, however, the impact of passive smoking on the cardiovascular system was also recognized almost 20 years ago, when evidence of the harmful effects of secondhand smoke (SHS) began to emerge.[8,9] In the past decade, clinical data from the Atherosclerosis Risk in Communities (ARIC) studies demonstrated that both active and passive smoking were associated with accelerated atherosclerosis progression as assessed by the increase in carotid artery intimal–medial thickness.[10] Moreover, Steenland[11] reported that the risk of death due to CVD increases by 30% in non-smokers who live together with smokers and another report from the United States suggested that more than 50 000 deaths annually from ischaemic heart disease are associated with SHS.[12] These findings, combined with experimental data which indicate that not only active smoking but also the passive exposure to secondhand smoke may exert detrimental effects on vascular homoeostasis,[13] are particularly alarming in view of the huge economic burden imposed on public health systems by CVD.[14,15]

Epidemiological data suggest a non-linear dose–response relationship between the intensity of exposure to SHS and the risk of ischaemic heart disease.[16,17] For example, the excess risk of developing CVD amounts to ~80% in active smokers at the age of 65, but it may also be as high as 30% in passive smokers.[18] Using measurements of the serum concentration of cotinine (a biomarker of smoke exposure) in a large prospective population study, Whincup *et al.*[19] recently concluded that the risk of coronary heart disease related to passive smoke exposure has probably been underestimated in earlier reports and might, in fact, be very close to the risk reported for active smokers. According to the conceptual model advanced by Glantz and Parmley[20] and further developed by Law and Wald,[21] this alarming observation may be related to the fact that some of the effects which cigarette smoke exerts on the cardiovascular system may already plateau upon exposure to

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very low doses and thus smoke exposure, even if passive, may be capable of maximally activating the pathological processes discussed subsequently. Besides, most of the well-described effects of passive smoking on vascular homoeostasis appear to be characterized by a rapid onset and can therefore be regarded as acute, even though SHS exposure at home or at the workplace almost always occurs on a regular, recurrent basis rather than being a single event. Importantly, this latter concept also implies that passive exposure to SHS has the potential to trigger acute cardiovascular events.[22–24]

A recently published article reviewed the epidemiological evidence which strongly supports the detrimental effects of secondhand smoke on the cardiovascular system.[25] The present review extends these findings and concentrates on our current state of knowledge regarding the pathomechanisms which mediate the impact of SHS on cardiovascular pathophysiology. We performed an extensive Pubmed search using specific key terms related to secondhand smoke (secondhand smoke, environmental tobacco smoke, sidestream smoke, passive smoking, and involuntary smoking) in combination with CVD (cardiovascular disease, coronary artery/coronary heart disease, mechanism, pathophysiology, and acute manifestation). The search also included the articles cited in the identified studies. A particular focus of our review is on how SHS-related endothelial dysfunction, platelet activation, oxidative stress, and inflammation may contribute to the acute clinical manifestations of coronary artery disease (*Figure 1*).

Components of secondhand smoke

In general, secondhand smoke has two main components, sidestream and mainstream smoke. Sidestream smoke emerges from the tip of a burning cigarette, accounting for 85% of the total amount of SHS. The remaining 15% are made up of mainstream smoke, which has been inhaled and is exhaled by an active smoker.[26,27] Importantly, the concentration of numerous toxins has been shown to be dramatically (up to 100-fold) elevated in sidestream smoke when compared with mainstream smoke, underscoring the potential adverse impact of SHS on health.[28] With regard to the physicochemical composition of SHS, a vapour phase and a particular phase can be distinguished. With regard to the latter, particles $<2.5\ \mu m$ are of special interest because they can be inhaled deeply into the lungs. The finding that particles in sidestream smoke are smaller than those in mainstream smoke supports the assumption that sidestream smoke may, in fact, be more dangerous than mainstream smoke.[28] So far, only few clinical and experimental studies have investigated the effects of specific components of SHS[29–31] and the overall impact of passive smoking on an organism probably has to be attributed to the complex mixture of SHS rather than to a specific component of cigarette smoke.

Impairment of endothelial function

The endothelium plays a central role in vascular homoeostasis, because it expresses and secretes a number of regulatory factors including nitric oxide or prostaglandins and is involved in the regulation of the vascular tone. Moreover, platelet aggregation, fibrinolysis, monocyte adhesion, and the proliferation of vascular smooth muscle cells are regulated by signalling molecules derived from endothelial cells.[32] In experimental in vivo studies, we and others described how injury to the endothelium triggers vascular remodeling and promotes neointimal growth,[33,34] and it is currently accepted that impairment of endothelial function predicts the initiation and progression of atherosclerosis.[35,36] Endothelial injury and activation result in the migration of monocytes into the vessel wall, their transformation into lipid-laden macrophages, and the subsequent growth and destabilization of lesions due to local inflammatory activity.[35]

Smoking, alone or in combination with other cardiovascular risk factors such as adiposity, diabetes mellitus, or hypercholesterolaemia, has been demonstrated to result in endothelial dysfunction. For example, *in vitro* studies showed that cigarette smoke condensate induces the surface expression of cell adhesion molecules and promotes the transendothelial migration of monocyte-like cells[37–40] and a 5-min exposure to the smoke of one research cigarette elicited the adhesion of leucocytes to endothelial cells in

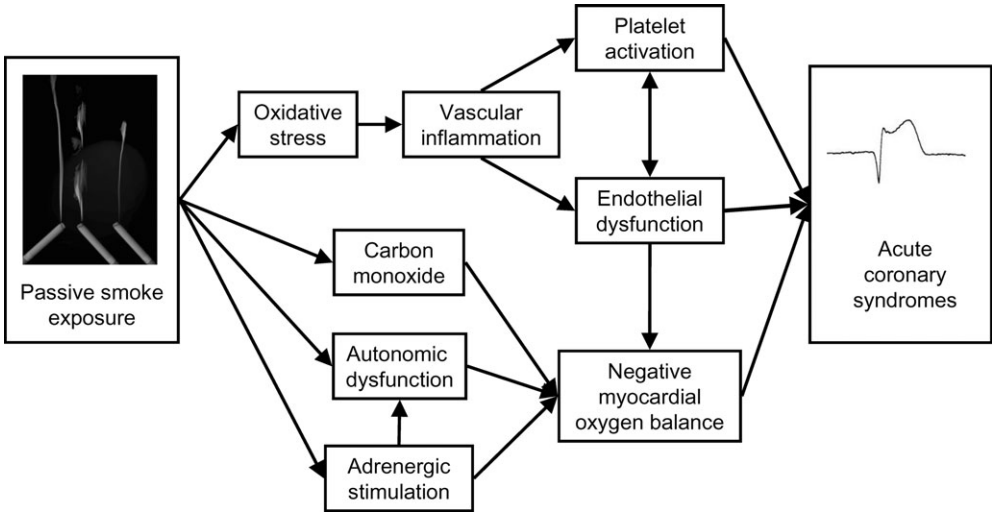

Figure 1 Mechanisms linking passive smoke exposure to acute clinical manifestations.

hamsters.[41] Clinical studies observed impaired endothelium-dependent vasorelaxation, the earliest sign of endothelial dysfunction, in smokers,[42–44] and active as well as passive smoking inhibited endothelium-dependent vasodilatation to a similar extent.[45] Moreover, Sumida *et al.*[46] found that passive smoking turns the acetylcholine-induced coronary artery relaxation into a vasoconstriction. In another study, coronary flow reserve, although higher in non-smokers than in active smokers under control conditions, was similar in the two groups after a 30-min exposure to SHS.[47] These findings indicate that the relatively low doses of toxins inhaled by passive smoking are sufficient to elicit a strong acute response. The agents and pathways responsible for these functional changes of endothelial function have not yet been completely elucidated, but they may be related, at least in part, to the inactivation of nitric oxide.[48] For example, animal studies suggested that passive smoking reduces the activity of endothelial NO synthase [possibly due to the action of carbon monoxide (CO)][49] and the endothelial arginine content.[50] In accordance with these results, it was shown that L-arginine supplementation prevents endothelial dysfunction induced by secondhand smoke in rabbits[50] and reduces the infarct size in SHS-exposed rats.[51]

Apart from functional changes, passive smoking may directly impair the viability of endothelial cells. Earlier studies described ultrastructural features of increased permeability and cellular damage in nicotine-exposed endothelial cells.[52,53] Regeneration of vascular endothelial layers and restoration of endothelial function are of central importance for vascular homoeostasis and atherothrombosis prevention, but endothelial repair is often limited due to the high degree of differentiation of this particular cell type.[54] Recently, interest focused on circulating endothelial progenitor cells (EPCs) as a possible mechanism of vascular protection and repair following oxidative stress and endothelial damage. Adult bone marrow contains a subtype of haematopoietic stem cells with the potential to differentiate into mature endothelial cells.[54,55] Interestingly, clinical studies recently reported that the presence of established cardiovascular risk factors including smoking is inversely correlated with the number and functional activity of circulating EPCs.[56,57] In fact, cotinine, a metabolite of nicotine, was shown to suppress the growth of haematopoietic progenitor cells at concentrations equivalent to its serum levels in smokers.[58] Accordingly, a history of cigarette smoking was associated with a reduced number and differentiation of circulating VEGF-R2-positive/CD34-positive cells,[59] whereas smoking cessation resulted in a rapid increase in their number in healthy male individuals.[60] Moreover, smoking during pregnancy reduced the number of haematopoietic progenitor cells in the umbilical vein blood of the newborn.[61] The possible impact of SHS on the mobilization and the circulating numbers of EPCs is an important issue that needs to be addressed by future trials.

Effects on platelet activation

Platelet activation and thrombosis at sites of vascular injury or atheromatous plaque disruption play a crucial role in the pathophysiology of acute coronary events.[5,62] Clinical and experimental studies found enhanced thrombosis and increased platelet aggregation in response to agonists in smokers.[63,64] Importantly, platelet α-granule constituents, such as platelet factor-4, β-thromboglobulin, and platelet-activating factor, are increased in the plasma of passive smokers, indicating ongoing platelet activation in these individuals.[13,65,66]

Active smoking is thought to elicit an adrenal epinephrine release, which is capable of enhancing platelet activation. In a discussion of the non-linear dose–response hypothesis relating smoke exposure to the risk of CVD, Smith *et al.*[67] concluded that serum nicotine concentrations usually found in passive smokers are not sufficient to induce significant epinephrine release and that platelet activation related to passive smoking may thus be mediated by alternative (or additional) mechanisms.

In a number of *in vitro* and *in vivo* studies, nicotine alone resulted in attenuation (rather than enhancement) of platelet activation.[30,68–70] Importantly, however, although nicotine does not, by itself, appear to promote platelet aggregation, only 20 min of passive exposure to whole smoke may suffice to induce activation of platelets to an extent comparable to that of active smoking of one to two cigarettes.[71] This fact points to a steep dose–response relationship for low SHS doses. Of note, although platelets of active smokers are already maximally activated, those of non-smokers appear to be susceptible to pro-aggregatory changes with every SHS exposure.[72] Using a modified prothrombinase method, Rubenstein *et al.*[30] compared the effects of sidestream and mainstream smoke on platelet function. Surprisingly, the impact of sidestream smoke was as pronounced as that of mainstream smoke, and it was even stronger for the so-called 'light' cigarettes. Studies in humans identified decreased platelet sensitivity to the anti-aggregatory actions of prostaglandin I_2 as at least one potential pathomechanism.[73] Moreover, passive smoking increases thromboxane formation,[74] probably due to nicotine-induced catecholamine release.[75] Clearly, further research is needed to identify and analyse the mechanisms of platelet activation as a result of SHS.

Apart from the direct effects of cigarette smoke on platelet function and thrombosis, the interaction of activated platelets with a dysfunctional, 'pro-coagulant' endothelium may be one of the mechanisms mediating the pro-atherothrombotic effects of passive (and active) smoking.[76–78] Moreover, elevated circulating levels of coagulation factors such as thrombin, tissue factor, and fibrinogen, are present in plasma of smokers when compared with non-smokers.[40,79–82] High plasma levels of plasminogen activator inhibitor (PAI)-1 may also contribute to an impaired fibrinolysis in smokers and are correlated with the estimated pack-years of cigarettes smoked,[83,84] although this latter mechanism has not yet been examined in a population of passive smokers.

Oxidative stress, lipoprotein modification, and inflammation

Exposure to SHS produces oxidative stress.[85–89] In addition to oxidants contained in cigarette smoke itself,[90] free radicals are also released endogenously from activated neutrophils. Importantly, whereas active smokers seem to be adapted to chronic oxidative stress and often exhibit an

elevated antioxidant enzyme activity,[91] passive smoking impairs antioxidant mechanisms in non-smokers.[47] In the presence of free radicals and increased oxidative stress due to passive smoke,[92,93] low-density lipoprotein (LDL) is converted to oxidized LDL, which, in turn, elicits a multitude of effects in the vessel wall. Apart from causing endothelial activation and dysfunction,[94] intramural oxLDL is taken up by local macrophages which thereby undergo activation and transformation into foam cells.[35,95] In humans, elevated levels of thiocyanate, a typical finding in passive smokers,[96] have been linked to an increased number of macrophages in atherosclerotic plaques.[97] Moreover, according to experimental data, even short exposure to SHS significantly increases lipid accumulation in the wall of perfused rat arteries.[98] Of note, polycyclic aromatic hydrocarbons (e.g. benzpyrene), which can be integrated into the plaque after binding to lipoprotein subfractions, also promote the proliferation of vascular cells and plaque progression.[99,100] *In vivo* studies in animal models of atherosclerosis demonstrated that passive cigarette smoking increases the size and lipid content of lesions in apolipoprotein E-knockout (apoE −/−) mice[101] and in cholesterol-fed rabbits.[102] Exposure to SHS was also shown to change the ultrastructure and mechanical properties of rat pulmonary arteries.[103] Finally, it needs to be mentioned that recent evidence in apoE −/− mice suggests that exposure to SHS very early in life (e.g. in neonates) may predispose to adult atherogenesis.[104]

Elevation of circulating inflammation markers (white blood cell count, C-reactive protein, homocysteine, and fibrinogen) was recently reported in passive smokers.[105] This adds to earlier findings of raised fibrinogen levels[106,107] and leukocyte counts accompanied by an activation of the immune cells[108] in response to SHS exposure. Thus, as passive smoking occurs on a regular basis in most individuals exposed to SHS, it is very likely to contribute to a persistent inflammatory response which promotes atherothrombosis.[109]

Further evidence for acute effects of secondhand smoke on the cardiovascular system

Passive smoking stimulates sympathetic nervous activity (measured as muscle sympathetic nerve activity[110]) and inhibits vagal efferents to the heart.[111] Nicotine may partly be responsible for these effects.[31,32,112–114] Moreover, it has been hypothesized that the odours prevailing in a smoke-filled room may initiate the release of catecholamines and stress hormones.[115] Smoke-related alterations of autonomic nervous function are supported by a decreased heart rate variability in passive smokers as reported by Pope *et al.*[116] In that study, the ECG of healthy non-smokers was continuously monitored for 8 h during which participants moved every 2 h between the smoking and the non-smoking areas of an airport. Secondhand smoke consistently and reversibly decreased heart rate variability. As autonomic dysfunction is linked to higher mortality rates in patients with chronic heart failure,[117] the authors speculated that such deleterious effects might result from passive smoking as well[116]. In contrast, although active smoking has been unequivocally shown to raise heart rate and arterial blood pressure,[118] the data on the effects of SHS on these parameters are still controversial.[27,28,110]

CO is a component of secondhand smoke and a marker of smoke exposure in the exhaled air. CO binds to haemoglobin and impairs the capacity of red blood cells to transport oxygen. In this regard, CO has been blamed for the reduction in exercise tolerance observed after passive smoking.[119] To date, CO is one of the few single substances which have been systematically studied in an attempt to explain the effects of SHS on the organism. However, the scarcity of data on the involvement of other possible mediators does not, by itself, justify the assumption that the impact of SHS on cardiovascular homoeostasis is solely (or mainly) attributable to carboxyhaemoglobin formation. Thus, oxygen utilization at the subcellular level may also be impaired by passive smoking, as suggested by a drop in the activity of the mitochondrial enzyme cytochrome oxidase following smoke exposure.[120] In addition to reduced oxygen transport capacity, coronary vasoconstriction due to adrenergic stimulation may further impair oxygen supply to the heart. At the same time, sympathetic activation increases cardiac afterload, thereby elevating the oxygen demand of cardiomyocytes. The resulting hypoxia lowers the threshold for cardiac arrhythmias in patients with coronary artery disease.[29] Moreover, exposure to SHS shortens the symptom-free interval in patients with stable angina.[22] In summary, several factors apart from a reduction in the oxygen-carrying capacity of the blood seem to mediate the acute effects of SHS on the cardiovascular system. Most probably, the mechanisms discussed earlier may synergistically impair cardiovascular function and give rise to clinical manifestations.

Maximal activation at low doses: linking experimental data to clinical evidence

In the study by Whincup *et al.*,[19] cotinine levels were related to the subsequent 20-year risk of suffering acute coronary events. In fact, it has been estimated that passive smoking elevates the overall risk of an acute cardiovascular event by 25–35%.[23] However, the CARDIO2000 trial[121] suggested that the excess risk for acute coronary syndromes may be considerably higher, rising to 97% in people exposed to SHS in their homes. This finding is in accordance with earlier reports from Argentina, Australia, and New Zealand.[122,123] Not surprisingly, Sargent *et al.*[24] recently reported a drop of hospital admissions for acute myocardial infarction by 40% following the enactment of a local law banning smoking in public and workplaces. Despite some limitations of this study (relatively small study population and no measurement of actual smoke exposure), the results indicate that passive smoking and the incidence of acute coronary syndromes may indeed be more closely related than traditionally thought. Clearly, further systematic research is needed to correlate parameters of actual SHS exposure with the occurrence of subsequent acute coronary events and thus clinically confirm (or reject) the notion, thus far derived from experimental data, that even very low doses of smoke exposure may

activate pathophysiological pathways, eventually leading to acute coronary syndromes.

Once an acute coronary syndrome occurs, the resulting damage to the heart might further be aggravated by ongoing passive smoking. Robinson *et al.*[124] already showed that the creatine kinase of active smokers suffering from myocardial infarction reached higher values than that of non-smokers, 15 years ago. Although an analogous study regarding passive smoking has not been conducted yet, data from studies in rats support the assumption that exposure to SHS increases infarct size.[13] Greater reperfusion injury due to free radicals[125] or activation of platelets[126] caused by passive smoking may be the underlying patho-mechanism.

Conclusion

Epidemiological evidence clearly indicates that passive smoking is linked to an increase in the incidence of CVD. Extensive clinical and experimental researches have revealed that the acute effects elicited by smoke exposure, including endothelial dysfunction, platelet activation, oxidative stress, and inflammatory reactions are involved in the pathogenesis of atherosclerosis (*Figure 1*). Importantly, passive smoking appears to be capable of precipitating the acute manifestations of CVD (atherothrombosis) and may also have a negative impact on the outcome of patients who suffer acute coronary syndromes. In view of the available evidence and the fact that SHS-related changes in vascular function are at least partly reversible, clinicians need to inform their patients about the risks associated with passive smoking and strongly support the enforcement of smoking bans in all public places.

Conflict of interest: none declared.

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