Immediate and short-term consequences of secondhand smoke exposure on the respiratory system

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Purpose of review

This review critically evaluates the existing biological evidence regarding the immediate and short-term respiratory consequences of secondhand smoke (SHS).

Recent findings

A 1-h exposure to SHS at bar/restaurant levels generates a marked inflammatory reaction and significant decrements on lung function. These deleterious effects of SHS are exacerbated when physical activity follows the SHS exposure, particularly in less fit individuals. The main respiratory effect mechanisms of SHS include a direct induction of growth factors resulting in airway remodelling and alterations in nitric oxide regulation. Pharmacological agents that increase either apical membrane chloride conductance or basolateral membrane potassium conductance may be of therapeutic benefit in patients with diseases related to SHS exposure. Moreover, treatment with statins has shown beneficial effects towards preventing the SHS-induced pulmonary hypertension, vascular remodelling, and endothelial dysfunction.

Summary

Based on recently discovered evidence, even brief and short-term exposures to SHS generate significant adverse effects on the human respiratory system. Future research directions in this area include the concentrations of tobacco smoke constituents in the alveolar milieu following SHS exposure, individual susceptibility to SHS, as well as pharmacological treatments for reversing the SHS-induced airway remodelling.

Keywords

airway remodelling, environmental tobacco smoke, inflammation, passive smoking, respiratory disease

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Introduction

The first evidence on the unfavourable health effects of secondhand smoke (SHS) arose in 1981 from a study showing that nonsmoking Japanese women married to men who smoked had an increased risk for lung cancer [1]. Since then, a multitude of papers have supported the unfavourable effects of SHS, most of which evaluated longitudinal epidemiological data, whereas exposure studies assessing the immediate and short-term SHS effects are limited. However, the latter information is essential and of the utmost importance for elucidating the underlying physiological mechanisms involved in SHS-induced system disruption [2,3].

Since the first study on SHS, research in this topic has spread into different areas and new scientific evidence continues to accumulate. Thus far, the cellular, animal, and human studies conducted indicate a number of mechanisms by which the deleterious effects of SHS on the respiratory system may arise. However, a recent review concluded that many germane studies incorporate limitations [4•]. For instance, a large number of epidemiological studies base SHS exposure on self-report without an objective measurement of exposure, they adopt a cross-sectional design, and they provide little data on the duration of the exposure. On the contrary, the majority of mechanistic exposure studies rely on animal models or in-vitro experiments both of which are inherently limited, particularly in relation to the level and duration of the exposures, as well as their relevance to humans. Nevertheless, the literature also contains wonderful experiments that have provided novel evidence on the underlying pathophysiological mechanisms related to the respiratory effects of SHS. The aim of this review is to critically evaluate the existing biological evidence regarding the immediate and short-term respiratory consequences of SHS.

Immediate and short-term secondhand smoke respiratory effects

Chronic lung disease is generally the result of long-term processes, yet even brief exposures to SHS appear to

initiate mechanisms that contribute to its development [5–8]. This notion is supported by evidence indicating a reduction in the incidence of respiratory symptoms among hospitality workers following the implementation of smoke-free laws in different countries [9–11]. Until recently, the immediate and short-term effects of SHS on the human respiratory system remained elusive, yet it is now known that even a 1-h exposure to SHS at bar/restaurant levels generates significant decrements on lung function. Specifically, the aforementioned SHS exposure causes a 10.8% decrease in forced expiratory volume in 1 s (FEV_1), an 11.8% decrease in FEV_1/forced vital capacity (FVC) ratio, as well as decrements of 11.4, 15.9, and 13.6% in maximum expiratory flow when 75, 50, and 25% of FVC remains in the lungs, respectively ($MEF_{75\%}$, $MEF_{50\%}$, and $MEF_{25\%}$) [12•]. This experiment was the first to investigate the duration of the immediate and short-term SHS effects on lung function and to demonstrate that it is linked with an intense inflammatory reaction. Moreover, the observed SHS-induced changes in FEV_1 and FEV_1/FVC ratio closely resembled the airway obstruction apparent in smokers [13], a notion that was further supported by the SHS-induced changes in $MEF_{75\%}$, $MEF_{50\%}$, and $MEF_{25\%}$ which showed a MEF–volume curve convex to the volume axis with an increasing curve in late expiration. Such results are typical for obstructive diseases such as cystic fibrosis, bronchial asthma and wheezy bronchitis [14]. Given the above findings, it was subsequently proclaimed that 'the evidence is now clear that SHS has a substantive role in causing chronic respiratory disease' [15].

Millions of nonsmokers suffer daily SHS exposures at home or at work, many of who then have to walk fast for several minutes or climb a few sets of stairs. For this reason, a recent experiment assessed the cardiorespiratory and immune response to physical activity following SHS, showing that the immediate and short-term respiratory effects of SHS are intensified when physical activity is involved [16•]. Indeed, results showed that a number of respiratory indices are markedly compromised for at least 3 h following a 1-h exposure to SHS, particularly in less fit individuals [16•]. For instance, decrements of 10.5% in FEV_1 and in FEV_1/FVC ratio were observed immediately following SHS. Three hours following the SHS exposure, the FEV_1 remained 8.1% lower compared to baseline. Moreover, an intense inflammatory reaction was observed immediately after the SHS exposure lasting at least 3 h thereafter. Taken together, these results show that moderate SHS exposures decrease lung function and produce a significant inflammatory reaction. Moreover, individuals that are briefly exposed to SHS and then have to become physically active may be at an increased risk for allergic and respiratory symptoms, especially those that are unfit.

Key points

- Even a 1-h exposure to SHS at bar/restaurant levels generates a marked inflammatory reaction and significant decrements on lung function.
- The respiratory and immune response to physical activity following 1 h of SHS is severely compromised for at least 3 h, particularly in less fit individuals.
- The main respiratory effect mechanisms of SHS are a direct induction of growth factors resulting in airway remodelling and alterations in nitric oxide regulation.
- Pharmacological agents that increase either apical membrane chloride conductance or basolateral membrane potassium conductance may be of therapeutic benefit in patients with diseases related to SHS exposure.
- Treatment with statins has shown beneficial effects towards preventing the SHS-induced pulmonary hypertension, vascular remodelling, and endothelial dysfunction.

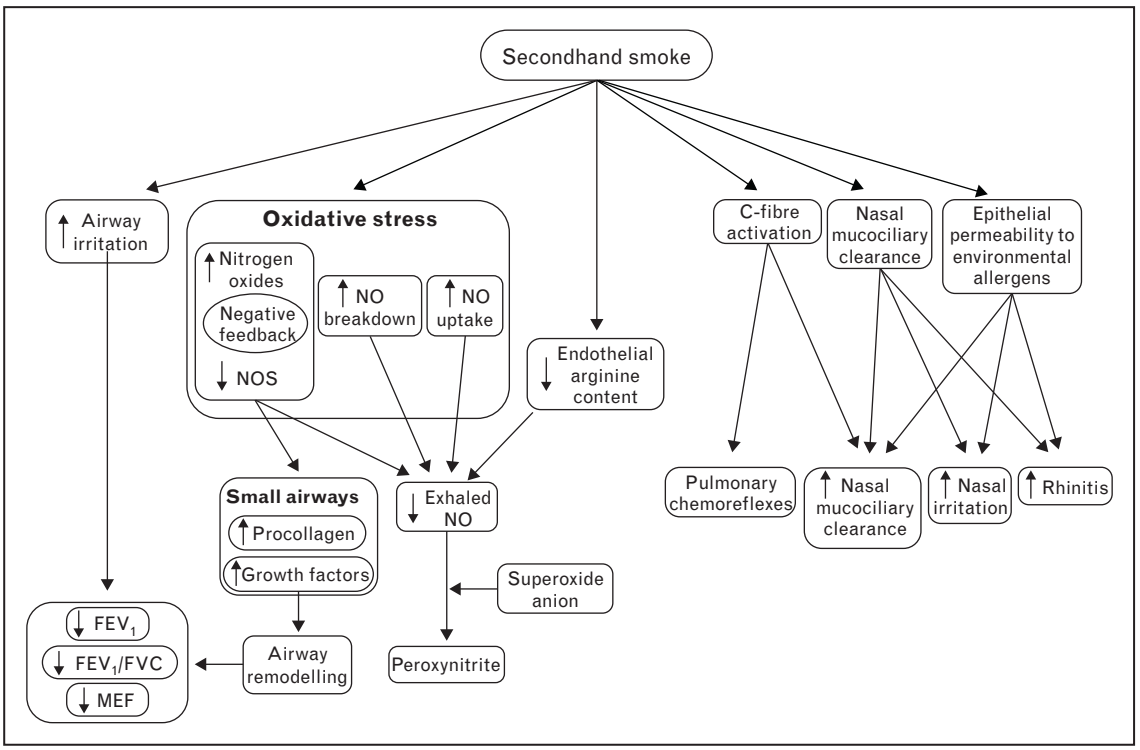
Length of secondhand smoke exposure

The available evidence has shown SHS-induced effects on the respiratory system within the first few minutes of smoke exposure [17,18]. Exposure for 5 min to the smoke of one cigarette elicits the adhesion of leucocytes to endothelial cells [19], whereas within the first 15 min of moderate SHS exposure there is a decline in exhaled nitric oxide levels [20]. Exposure of 1 h to moderate SHS is accompanied by marked decrements in FEV_1 and FEV_1/FVC ratio [12•,16•], as well as marked changes in interleukins 1 beta, 4, 5, and 6, tumour necrosis factor alpha, and interferon gamma [6,12•]. Two hours of moderate exposure to SHS results in the development of nasal congestion, irritation, and increased rhinitis [21]. Exposures to SHS for up to 3 h causes marked changes in leucocyte counts accompanied by an immune cell activation [22]. SHS exposures for up to 5.5 h are accompanied by increased oxidative stress [23–25], whereas every-day SHS exposures induce vascular remodelling in 1 month and emphysema in 3 months [26].

Immediate and short-term secondhand smoke respiratory effect mechanisms

The immediate and short-term effects of SHS on the respiratory system are illustrated in Fig. 1. Inhalation of cigarette smoke elicits acute pulmonary chemoreflexes, characterized by apnoea, bradycardia, and hypotension through activation of pulmonary C fibres [18]. Moreover, the mechanism behind the acute SHS-induced airflow restriction presented in the previous section can be related to airway irritation, given that SHS elicits irregular breathing patterns, cough reflex, and bronchoconstriction

Figure 1 The immediate and short-term effects of secondhand smoke on the respiratory system



NO, nitric oxide; NOS, NO synthase; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MEF, maximum expiratory flow. Adapted with permission [4•].

through the activation of vagal afferents [27]. Yet, airway irritation may not be the only mechanism underlying the initial response to cigarette smoke, as other lines of evidence suggest that SHS induces rapid profibrotic growth factor production as well as production of type 1 procollagen within the walls of small airways through an oxidant mechanism [17]. These findings indicate that the initial response to cigarette smoke may reflect direct induction of growth factors resulting in airway remodelling. Smokers demonstrate various types of airway remodelling in the large and small airways, including fibrosis, muscle hyperplasia, and mucous metaplasia/hypersecretion. Fibrosis and the thickening of the airway wall, particularly in the subepithelial compartment within the small airways, are part of the pathogenesis of SHS-induced airflow limitation [28], yet the precise effect of airway remodelling on airflow obstruction remains to be determined [17,29].

Recent animal studies demonstrated an induction of lung emphysema by alveolar wall destruction after 20 weeks of SHS exposure [30••] that is probably mediated by interleukin 1 beta [31••]. The SHS-induced murine emphysema is not reversible with smoking cessation [30••], in line with smoking cessation findings in humans where the alveolar enlargement and destruction seen in lung emphysema is generally thought to be irreversible [32•,33]. However, extrapolation of these results to humans must be made with caution because it is not clear how the murine models translate into human pathophysiology. For instance, although removal of tumour necrosis factor alpha signalling substantially ameliorates emphysema in the mouse, thus far trials of tumour necrosis factor alpha antagonists have not been successful in humans [34].

The acute SHS-induced airflow restriction may be also a consequence of alterations in nitric oxide regulation. Indeed, as mentioned in the previous section, within the first 15 min of moderate SHS exposure there is a decline in exhaled nitric oxide levels [20], confirming similar in-vitro findings [35]. This is noteworthy, as changes in the production of nitric oxide are implicated in the pathophysiology of airway diseases associated with smoking [36]. Nitric oxide reacts rapidly with superoxide anion, producing the deleterious oxidant peroxynitrite, a mechanism similar to that observed in cystic fibrosis where nitrite levels, indicators of nitric oxide oxidative metabolism, are elevated in breath condensate of afflicted persons but exhaled nitric oxide is not [37]. The drop in exhaled nitric oxide levels within the first minutes of SHS exposure may be caused by the

decreased expression of nitric oxide synthase through the mechanism of feedback inhibition, given the high concentrations of nitrogen oxides inherent in tobacco smoke [38]. Other possible mechanisms include an increased breakdown or modification of nitric oxide by SHS oxidants, or a SHS-induced accelerated uptake of nitric oxide [39].

Clinical implications

Available evidence has shown that moderate SHS exposure causes nasal congestion, irritation, and increased rhinitis within 2 h of exposure [21]. A number of potential mechanisms have been examined [40], and research to date shows that nasal mucociliary clearance [41], C-fibre activation [42], and epithelial permeability to environmental allergens [43] are the most likely candidates which may explain the clinical effects of brief SHS exposure on the respiratory system.

Acute SHS exposure is a significant risk factor for respiratory diseases, including lower airways infections, middle ear infection, chronic rhinosinusitis, and asthma in adults [44], as well as asthma and more severe respiratory syncytial virus infection in children [45]. Although these diseases are clearly multifactorial in nature, they all share a component of impaired mucociliary clearance and mucus retention. The preservation of normal mucociliary clearance in the respiratory tract depends on salt and water transport by respiratory epithelial cells, yet SHS can inhibit epithelial chloride secretion [46,47] potentially through an oxidative mechanism [48] or a decreased basolateral membrane K^+ conductance [47]. Consequently, pharmacological agents that increase either apical membrane chloride conductance or basolateral membrane potassium conductance may be of therapeutic benefit in patients with diseases related to SHS exposure.

Exposure to SHS acutely promotes the production of inflammatory cytokines [16•,12•] that are closely associated with the chronic lung inflammation and structural changes observed in pulmonary disease patients [49]. Based on these findings, it has been recently suggested [12•] that chronic SHS may have clinical implications such as increased susceptibility to infection, chronic lung inflammation as well as pathological airway changes including chronic obstructive pulmonary diseases. Indeed, the SHS-induced production of inflammatory cytokines such as interleukins 5 and 6 as well as interferon gamma has been linked with marked decrements in FEV_1 and FEV_1/FVC ratio [16•,12•], confirming the association between circulating inflammation markers and FEV_1 [50]. In turn, lower FEV_1 and FEV_1/FVC ratio are associated with a greater prospective risk of cardiovascular mortality amongst nonsmokers [51]. Moreover, the finding that inflammatory cytokine levels remain elevated for at least 3 h following SHS exposure allude to chronic low-grade systemic inflammation in individuals exposed to SHS on a daily basis and/or at higher smoke concentrations. This is particularly true for the case of interferon gamma [12•], which is closely linked with chronic obstructive pulmonary disease and asthma [52]. At present, the physiological mechanisms linking low-grade systemic inflammation and pulmonary disease are not entirely understood [53]. However, a number of studies have reported higher levels of systemic fibrinogen and C-reactive protein in individuals with impaired lung function [54] and in patients suffering from chronic obstructive pulmonary disease [55].

As described above, previous research has shown that SHS exposure induces vascular remodelling in 1 month and emphysema in 3 months [26]. A very interesting study published recently employed a relatively late intervention with simvastatin, starting at month 3 of a 6-month SHS exposure protocol, and found that the statin therapy reversed the SHS-induced pulmonary hypertension, vascular remodelling, and endothelial dysfunction [56••]. However, although the treatment with simvastatin prevented the development of emphysema, it did not protect against small airway remodelling. These beneficial effects of statins towards reducing emphysematous lung destruction have been ascribed to decreasing neutrophil migration, cytokine production, and oxidant damage [56••]. Statins were originally used as first-line therapy in patients with cardiovascular disease for lowering cholesterol levels and improving peripheral vascular perfusion, yet they have a wide range of other biologic effects including modulation of endothelial function, down-regulation of inflammation, modification of vascular wall structure, and amelioration of oxidative stress [57]. With regards to SHS-induced respiratory damage, previous reports suggested that statins may improve chronic obstructive pulmonary disease (COPD) mortality [58], especially mortality related to exacerbations [59], pulmonary function [60], exercise tolerance [61], inflammatory markers, and pulmonary artery pressure [62].

Conclusion

Based on recently discovered evidence, even brief and short-term exposures to SHS generate significant adverse effects on the human respiratory system. A 1-h exposure to SHS at bar/restaurant levels generates a marked inflammatory reaction and significant decrements on lung function. These deleterious effects of SHS are exacerbated when physical activity follows the SHS exposure, particularly in less fit individuals. The main respiratory effect mechanisms of SHS include a direct induction of growth factors resulting in airway remodelling and alterations in nitric oxide regulation. Pharmacological agents that increase either apical membrane chloride

conductance or basolateral membrane potassium conductance may be of therapeutic benefit in patients with diseases related to SHS exposure. Moreover, treatment with statins has shown beneficial effects towards preventing the SHS-induced pulmonary hypertension, vascular remodelling, and endothelial dysfunction. Notwithstanding the recent attention on the biological effects of brief SHS exposures and the excitement for the new discoveries in this area, we remain largely naive to issues as critical as the concentrations of specific tobacco smoke constituents following SHS exposure in the alveolar milieu as well as the interactions among the various constituents of SHS. Furthermore, future research should address individual susceptibilities, an approach that will lead to the recognition of genetic profiles that influence susceptibility to adverse SHS-induced effects and will provide insights into the underlying mechanisms of the health consequences.

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