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Hans汉斯

二手烟暴露与缺血性脑血管病的相关研究进展

宋士青

山东大学齐鲁医学院，山东 济南

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摘　要

二手烟(Secondhand smoke, SHS)暴露是威胁全球公众健康的重要环境风险因素，其与脑血管疾病的关联及机制研究对疾病防控意义重大。目前，吸烟在动脉粥样硬化疾病中的危害性已得到广泛的证实，而SHS的危害性被忽视了。SHS暴露与缺血性脑血管病发生发展的相关性以及具体作用机制仍需深入研究。本文对SHS的理化特性、流行病学特征及其促动脉粥样硬化与血栓形成的分子机制进行综述，整合临床证据，以期为缺血性脑血管病防治提供理论依据。

关键词

二手烟，卒中，缺血性脑血管疾病，动脉粥样硬化

Research Progress on Secondhand Smoke and Ischemic Cerebrovascular Disease

Shiqing Song

Cheeloo College of Medicine, Shandong University, Jinan Shandong

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Abstract

Secondhand smoke (SHS) exposure is a critical environmental risk factor threatening global public health, and elucidating its association with cerebrovascular diseases and underlying mechanisms holds significant implications for disease prevention and control. While the detrimental effects of active smoking on atherosclerotic diseases have been widely established, the hazards of SHS remain underrecognized. The correlation between SHS exposure and the development of ischemic cerebrovascular diseases, as well as its specific pathogenic mechanisms, require further investigation. This review synthesizes current knowledge on the physicochemical properties of SHS, its epidemiological characteristics, and molecular mechanisms promoting atherosclerosis and thrombosis. By

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integrating clinical evidence, we aim to provide a theoretical foundation for advancing strategies in ischemic cerebrovascular disease prevention and management.

Keywords

Secondhand Smoke, Stroke, Ischemic Cerebrovascular Disease, Atherosclerosis

1. 绪论

根据世界卫生组织(World Health Organization, WHO)的定义，二手烟(secondhand smoke, SHS)是指非吸烟者吸入燃烧端释放的侧流烟雾与吸烟者呼出的主流烟雾混合形成的复合污染物[1]。全球约 33%的非吸烟者长期暴露于 SHS 环境，发展中国家部分地区的暴露率甚至超过 50%，这种广泛暴露导致全球 1%的总死亡率，已成为重大公共卫生问题[2]。随着我国人口老龄化的加剧，脑血管疾病的发病率持续上升，已成为威胁公众健康的主要问题。研究表明，如果不及时采取预防措施，预计脑血管病的医疗总费用将增加一倍[3]。鉴于 SHS 暴露的广泛性及其毒性组分的致病特性，深入解析其与脑血管疾病的相关性及其机制对完善疾病防控体系具有重要价值。在本综述中，我们旨在阐述 SHS 的定义及其化学成分，回顾现有文献中有关 SHS 对动脉粥样硬化和血栓形成影响的研究、SHS 暴露与缺血性脑血管病相关性的人群研究，探讨当前有关 SHS 暴露与脑血管疾病关联及其在发病机制中的作用。

2. SHS 的理化特性及流行病学特征

2.1. SHS 的化学组成及危害

吸烟者吸入的烟雾被称为主流烟雾。SHS 是吸烟者呼出的少量主流烟雾(15%)和侧流烟雾(85%)的混合物[4]。SHS 烟雾中已发现 5300 余种化学成分，其中包括一氧化碳、氢氰酸、苯系物等 250 种毒性气体，以及铅、砷、镉等多种致癌性金属颗粒[5] [6]。值得关注的是，侧流烟雾中含有的有毒气态化学物质(如多环烃和挥发性亚硝胺)浓度显著高于主流烟雾[7]。SHS 包含气溶胶化的化学成分，这些成分存在于亲水或疏水的蒸汽相中。其亲水蒸汽相的成分易被上呼吸道吸收，而疏水成分则更可能进入肺部[8]。小于 2.5 微米的颗粒被称为可吸入悬浮颗粒，它们能够被吸入肺实质深处。根据侧流烟的空气稀释程度，SHS 中颗粒的浓度可从几微克到每立方米 300~500 毫克不等。有研究认为，SHS 的短期暴露(数分钟至数小时)即可产生与长期主动吸烟相当的生物学效应[9] [10]。

2.2. SHS 暴露评估方法

SHS 暴露的量化主要通过两类方法，一类是通过问卷调查收集参与者自我报告的暴露，另一类为对烟草代谢标志物进行检测。通过问卷采集暴露强度的各项数据，包括暴露源的吸烟强度(如同住吸烟者的日吸烟量)、吸烟者吸烟状态(如室内通风条件、家庭内是否允许吸烟)。儿童群体的研究常以父母吸烟状态作为暴露评估指标[11]。另外，一些研究选择采集被动吸烟者的每日暴露时长、累积暴露年数等来构建剂量－效应模型[12]。在目前的研究中，暴露场所一般分为家庭内暴露及家庭外暴露，家庭外暴露又分为工作场所的暴露和其他公共场所的暴露[13]。另外，SHS 暴露还可通过生物标志物进行评估。可替宁是尼

古丁的代谢产物，检测其在尿液、唾液或血液样本中的浓度水平可客观反映 SHS 的暴露程度[14]。该方法准确性较高，但因检测成本及操作复杂性限制，大规模流行病学研究仍以采集自我报告的 SHS 暴露为主。已有多项研究对使用自我报告评估与可替宁测量结果进行比较，结果表明其可靠性与有效性中等至良好[15] [16]。然而，也有研究表明，基于问卷的 SHS 暴露评估可能会错误分类或低估暴露量[16]。

2.3. SHS 的流行病学特点及疾病负担

WHO 在中国的调查显示，在非吸烟者中，68.1%的人暴露于 SHS。在空间分布特征方面，家庭环境(44.9%的非吸烟者报告)及公共场所(如网吧 89.3%、餐厅 73.3%)是主要暴露源，工作场所暴露率亦达 50.9% [1]。全球疾病负担研究证实，SHS 每年造成约 88 万非吸烟者死亡[17]，1990~2019 年期间，SHS 暴露导致的主要疾病有缺血性心脏病、慢性阻塞性肺疾病和卒中[18]。经济负担分析表明，2000~2010 年间中国因家庭 SHS 暴露产生的直接医疗成本累计达 86 亿美元[19]。

自 2007 年 WHO 颁布的《烟草控制框架公约》第 8 条建议实施无烟政策以来，全球范围内的公共场所、工作场所和交通工具中的吸烟禁令逐渐普及[1]。然而 1990~2019 年全球疾病负担数据显示，尽管无烟立法覆盖率逐步提升，仍有 79%的全球人口未受到无烟立法的保护[20] [21]，且不足 50%的国家制定了全面无烟立法[22] [23]。在中国，尽管公众对吸烟危害的认知度有所提升，但其知晓率仍处于较低水平：仅 36.4%的受访者知晓吸烟与卒中、心脏病及肺癌的关联性，而了解 SHS 导致成人心脏病、肺癌及儿童肺部疾病的比例仅为 36.1%。值得关注的是，超过 90%的公众支持公共场所全面禁烟政策，支持在不同公众地方禁烟的比率略有不同，吸烟者的支持度略低于非吸烟者[1]。

3. SHS 与脑血管疾病的临床证据

3.1. SHS 与卒中

在多个种族的男性和女性中进行的多项研究已经证明了卒中与 SHS 之间的相关性[24]-[27]。一项 Meta 分析显示，SHS 暴露使总体卒中风险增加 35% (RR = 1.35, 95% CI: 1.22~1.50) [28]，这一结果在多项剂量反应研究中得到进一步支持。何等人对从不吸烟的女性进行分析，发现了类似的剂量反应关系，即暴露量增加(以每天吸烟数量和分钟数衡量)，与缺血性卒中的患病率增加相关[29]。Oono 团队通过荟萃分析证实 SHS 与卒中之间存在非线性剂量反应关系，每日接触 40 支烟等效暴露者的卒中风险达峰值(HR = 1.56, 95% CI: 1.25~1.96)，即使每日仅暴露于 5 支烟等效剂量仍存在显著关联；两者之间存在因果关系[30]，其剂量反应曲线与心血管疾病研究中的拐点特征一致，可能与白细胞 DNA 加合物饱和度相关[31] [32]。在对于性别的亚组分析表明，无论男女，暴露于 SHS 的人群中卒中风险显著增加，女性风险高于男性(RR = 1.43 vs RR = 1.40)，但无统计学差异[28]。在李和福雷的系统综述对性别进行的亚组分析与上述研究得出了一致的结论[33]。尽管多数证据支持 SHS 与卒中的关联，仍有部分研究未观察到显著相关性[34]。另外，仅有部分研究对不同卒中亚型进行了分析，未来还需要更多的研究进一步明确 SHS 与不同卒中亚型的相关性。

3.2. SHS 与颈动脉斑块或颈动脉内中膜厚度

SHS 暴露与颈动脉粥样硬化发展的相关性已通过多维度研究得到证实。颈动脉内膜中层厚度(carotid intima-media thickness, cIMT)增厚一直是动脉粥样硬化发展的有效预测指标[35] [36]。Yang 和 Kallio 团队通过血液可替宁浓度检测，证实高暴露组儿童 cIMT 值显著高于低暴露组[37] [38]。芬兰心血管风险的前瞻性研究显示，父母均吸烟的青少年成年后的 cIMT 高于父母均不吸烟的成年期 cIMT，且该关联独立于血脂、血压等传统危险因素[39]。成人暴露研究中，此关联显示出剂量–效应关系。队列研究对 cIMT 的

变化进行评估，发现中年群体每周 10 小时，SHS 暴露持续 3 年，动脉粥样硬化进展加速 20% [40]；Gac 等人使用计算机断层扫描血管造影术对高血压且从不吸烟的患者进行了研究，他们发现，对于接受药物治疗的原发性高血压患者，与不暴露者相比，SHS 暴露与更严重的颅外动脉粥样硬化有关，表现为出现非钙化斑块和混合斑块的动脉段数量增加[41]。尽管存在个别负相关报道[42]，但多方法学证据一致表明，SHS 暴露通过促进 cIMT 增厚对心脑血管系统造成不可逆损害。这些发现跨越儿童期到成年期的暴露窗口，凸显了 SHS 防控在动脉粥样硬化一级预防中的关键作用。

4. SHS 促进动脉粥样硬化与血栓形成的分子机制

动脉粥样硬化和血栓形成是动脉闭塞的前兆事件，而动脉闭塞是缺血性卒中发生的机制。动脉粥样硬化是动脉壁内斑块形成以及随后动脉硬化开始发展的过程。其起始于分子层面的变化，主要发生在动脉壁最内层的内膜层。内膜层由一层内皮细胞构成，将动脉管腔与内膜下层(包括中膜和外膜)分隔开。内皮损伤及其随后的功能障碍导致脂蛋白渗入内膜下层。氧化修饰的脂蛋白触发单核细胞趋化形成泡沫细胞，伴随平滑肌增殖及炎症介质浸润，最终形成纤维斑块[43] [44]。血栓形成是血栓形成并导致其所在血管阻塞的过程。止血功能紊乱可通过多种机制发生，包括内皮细胞损伤、血流停滞或紊乱以及血液高凝状态。斑块破裂暴露促凝物质引发以下两个过程：初级止血过程是指血小板黏附于内皮损伤部位并聚集形成血小板栓子；次级止血是指通过凝血级联激活生成纤维蛋白网。上述过程导致血管闭塞，构成心脑血管事件的核心机制[44]。目前的研究表明，SHS 主要通过以下途径促进动脉粥样硬化和血栓形成过程。

4.1. SHS 诱导内皮细胞血管舒张功能障碍

内皮依赖性血管舒张(endothelium-dependent vasodilation, EDV)功能障碍是动脉粥样硬化发生的早期关键事件，其与一氧化氮(NO)介导的血管舒张功能失调密切相关。生理状态下，内皮细胞通过合成释放 NO 维持血管稳态[45]，而 SHS 暴露可显著破坏这一过程。临床研究证实，健康非吸烟男性暴露于 SHS 后，冠状动脉血流储备(充血与基础血流速度比值)从基线 4.4 ± 0.91 急剧下降至 3.4 ± 0.73，提示 EDV 功能严重受损[46]。值得注意的是，被动吸烟者与主动吸烟者表现出相似的 EDV 损伤程度[46] [47]。而部分研究观察到被动吸烟者的 EDV 损伤可能更为显著[47]，提示 SHS 可能具有独特的致病特征。

分子机制研究表明 SHS 通过多途径损害内皮稳态：1) 酶活性异常：年轻被动吸烟者的内皮细胞中，内皮型一氧化氮合酶(eNOS)表达量降低 37% ($P = 0.04$)，其磷酸化激活水平下降 65% ($P = 0.02$) [48]。Barua 团队创新性采用吸烟者血清培养模型，发现该处理可显著降低人脐静脉和冠状动脉内皮细胞的 NO 生成(分别减少 43%和 51%)，此效应与 eNOS 表达及活性调控直接相关[49] [50]；2) 结构完整性破坏：暴露于 SHS 20 分钟即可升高循环内皮细胞残骸水平[51]，引发血管通透性异常升高，这一病理改变与动脉粥样硬化发生发展密切相关[10]。需要特别指出的是，NO 作为多功能信号分子，不仅调控血管张力，同时参与抑制炎症反应、调节白细胞黏附等关键生理过程[52]。因此，SHS 导致的 NO 合成紊乱可能通过多机制协同作用，在损害血管舒张功能的同时，加速动脉粥样硬化进程并增加血栓形成风险。

4.2. SHS 与炎症激活

炎症反应是动脉粥样硬化开始和发展的关键因素[43]。动脉粥样硬化多种族研究(MESA)对 5000 多名不吸烟且接触 SHS 的成年人进行分析，结果表明，每周 SHS 暴露 ＞12 小时的参与者高敏 C 反应蛋白升高 13% (95% CI: 1.02~1.26) [53]，进一步佐证了 SHS 的全身性促炎作用。亚当斯等通过静脉内皮细胞检测发现，与未暴露者相比，SHS 暴露人群的核因子-κB (nuclear factor kappaB, NF-κB)活性显著升高($P = 0.007$)，且被动吸烟者与主动吸烟者的 NF-κB 水平无统计学差异[48]。动物实验表明，与未暴露的对照组、

每天暴露 60 分钟的对照组相比，每天暴露 120 分钟的 SHS 引发 IL-6、随后肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)等促炎因子上升($P < 0.05$) [54]。袁等研究发现，SHS 暴露诱导白细胞介素-12 水平升高，随后 TNF-α 表达增加。TNF-α 表达及 SHS 暴露均可进一步刺激单核细胞趋化蛋白-1 分泌，募集单核细胞至血管壁并促进氧化脂质沉积，从而形成动脉粥样硬化斑块的前体[55]。上述证据共同表明，SHS 通过多途径激活并放大炎症级联反应，推动动脉粥样硬化进程。

4.3. SHS 与血脂代谢紊乱

SHS 可通过对血脂谱的影响促进动脉粥样硬化。在一项针对约 3000 名健康女性的研究中，SHS 暴露与血糖和血脂状况的不良影响相关[56]。女性长期高剂量 SHS 暴露者(连续 6 个月、每周 4 天、每天至少 6 小时)的高密度脂蛋白胆固醇(HDL-C)、HDL2 亚型及载脂蛋白 A-I 水平显著低于未暴露者($P < 0.05$)，而 HDL-C 每降低 1 mg/dL 可使冠心病风险增加 2%~3% [57]。纽菲尔德等人对由于遗传性血脂异常早发性心脏病高风险的儿童进行的研究有类似的发现，这些儿童在接受家庭 SHS 暴露后 HDL-C 水平显著降低，与家庭成员戒烟后血流介导的舒张功能的可逆性不同，这种影响并不会出现逆转[58]。一项对 SHS 急性暴露的研究显示，非吸烟者接触 SHS 仅 30 分钟即可引发脂质过氧化加速、血清抗氧化能力下降及巨噬细胞低密度脂蛋白胆固醇蓄积[59]。而在长期暴露的动物实验中，载脂蛋白 E 缺陷小鼠经 14 周 SHS 暴露后，主动脉病变面积增加 3.3 倍($P < 0.001$) [60]。

4.4. 血小板功能与凝血级联激活

被动吸烟与急性血栓形成之间的相关性已得到证实。有研究表明，SHS 暴露 20 分钟即显著升高血小板活化水平，活化程度与主动吸烟 1~2 支相当[61]。纤维蛋白原是一种已知血栓形成的危险因素。一项来自日本的人群研究显示，校正混杂因素后，被动吸烟者的纤维蛋白原水平显著高于非暴露者[62]，这一趋势在暴露于家庭吸烟环境的青少年群体中同样存在[63]。巴鲁阿团队通过体外实验评估了吸烟者吸入烟草对凝血系统的影响，采用血栓弹力图分析凝血动力学，结合 GP IIb/IIIa 受体抑制法和电子显微镜观察，发现急性香烟烟雾暴露可显著缩短纤维蛋白形成时间(凝血启动加速)并增强凝血块结构强度(机械稳定性提升)，为解释吸烟者动脉粥样硬化斑块血栓形成倾向增加提供了直接机制证据[64]，这种倾向在 SHS 暴露的影响中可能也发挥着一定的作用，需要进一步证实。上述效应与斑块破裂协同作用，最终导致急性血管事件[65]。

5. 小结与展望

现有证据表明，SHS 通过内皮损伤、氧化应激、炎症激活及凝血紊乱等多通路协同促进动脉粥样硬化血栓形成。其致病效应无安全阈值，即使低水平暴露仍可产生显著风险。尽管全球无烟政策覆盖率逐步提升，但立法执行力与公众认知度仍存差距。未来研究对于阐明 SHS 与出血性卒中、颅内动脉粥样硬化之间的关联性还有待进一步验证。另外，制定基于生物标志物及自我报告的个体化暴露风险评估标准、探索内皮保护或抗炎通路的干预策略需要进一步的研究探索。实现“零 SHS 暴露”的终极目标，需要政府、医疗机构与公众的协同努力，包括强化公共场所禁烟立法、推广家庭无烟环境建设及开展针对性健康宣教等。

利益冲突

所有作者均声明不存在利益冲突。

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