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颗粒物与超微颗粒致心肌梗死机制的研究进展*

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[摘要]　颗粒物是空气污染的重要组成部分,其来源包括工业排放、机动车尾气等。随着工业化和城市化的快速发展,空气污染问题日益严重,颗粒物对健康的危害也引起了广泛关注,尤其是其对心血管系统的影响。颗粒物根据其粒径大小可分为粗颗粒、细颗粒和超微颗粒。其中,超微颗粒由于其极小的粒径和较大的比表面积,能够深入肺部并进入血液循环,对心血管系统产生明显影响。该文回顾了近年来关于颗粒物与心血管疾病关系的相关文献,探讨了颗粒物尤其是超微颗粒导致心脏病发作的潜在机制,尝试性地提出了未来可能的研究方向。

[关键词]　心肌梗死;颗粒物;超微颗粒;氧化应激;炎症反应
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Research progress on the mechanism of myocardial infarction induced by particulate matter and ultrafine particles*

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[**Abstract**]　Particulate matter is an important component of air pollution,with sources including industrial emissions and motor vehicle exhaust. With rapid industrialization and urbanization,air pollution has become increasingly severe,drawing widespread attention to the health hazards of particulate matter,particularly its effects on the cardiovascular system. Particulate matter is categorized by particle size into coarse particles,fine particles,and ultrafine particles. Due to their extremely small size and large specific surface area,ultrafine particles can penetrate deep into the lungs and enter the bloodstream,exerting significant impacts on the cardiovascular system. This review examines recent literature on the relationship between particulate matter and cardiovascular diseases,explores the potential mechanisms by which particulate matter-especially ultrafine particles-triggers myocardial infarction,and suggests potential future research directions.

[**Key words**]　myocardial infarction;particulate matter;ultrafine particles;oxidative stress;inflammatory reaction

研究表明,暴露于颗粒物及超微颗粒会增加心血管疾病(cardiovascular disease,CVD)的发病率和病死率[1],超微颗粒还会提高既往心肌梗死患者的复发风险[2]。流行病学证据也表明,超微颗粒会增加心肌梗死风险[3-4]。尽管目前颗粒物及超微颗粒导致心脏病发作的具体机制尚不完全清楚,但已有研究数据支持氧化应激、炎症反应和心血管毒性。本文旨在分析和总结近年来的相关研究,探讨颗粒物及超微颗粒导致心脏病发作,尤其是心肌梗死发作的潜在机制,用于帮助高危人群制订预防策略,指导环境颗粒物暴露的心肌梗死患者的治疗,深化公众对颗粒物及超微颗粒对心血管健康影响的认识。

1　颗粒物及超微颗粒

颗粒物是空气污染的主要成分,按其直径可分为粗颗粒物、细颗粒物和超微颗粒,超微颗粒直径<100 nm,通常为化石燃料燃烧和工业排放的副产品[5]。柴油尾气中富含超微颗粒,常用于研究其危害[6]。超微颗粒直径小,能深入肺泡,甚至部分可穿过肺泡-毛细

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血管屏障进入血液循环，且其具有较大的比表面积，能携带更多化学物质和金属颗粒[7]。进入人体后，颗粒物及超微颗粒可引发全身炎症、内皮功能障碍和凝血功能异常，增加缺血性心脏病风险[8]。

2 潜在机制

心肌梗死是心脏供血突然中断导致的紧急病症，常见症状有胸痛、呼吸急促等。它通常由动脉斑块破裂引发，进而导致心肌缺氧受损，最终坏死。目前学界已提出许多机制，如炎症反应、氧化应激、斑块形成等[9]。暴露于颗粒物（包括超微颗粒）可直接或间接损伤心血管系统[10]。根据机制的不同可将致病途径分为直接和间接途径[11]。直接途径是指因氧气的作用直接导致心肌、血管功能障碍和钙离子失衡，而间接途径则是通过自主神经系统（automatic nerves system，ANS）和炎症反应来影响心血管系统[12-14]，见图 1、2。

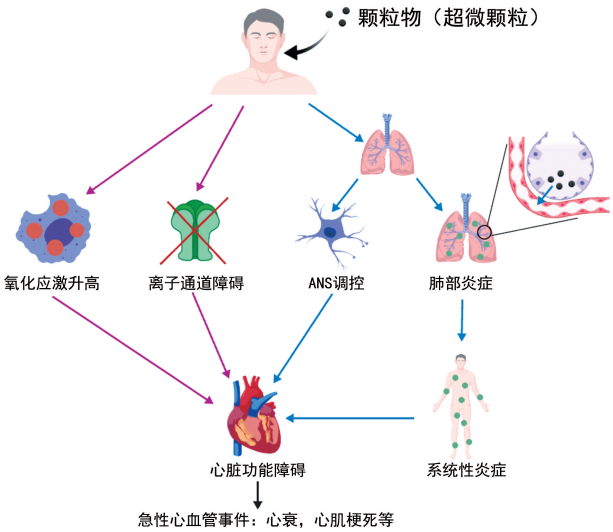

图 1 颗粒物导致急性心血管事件途径

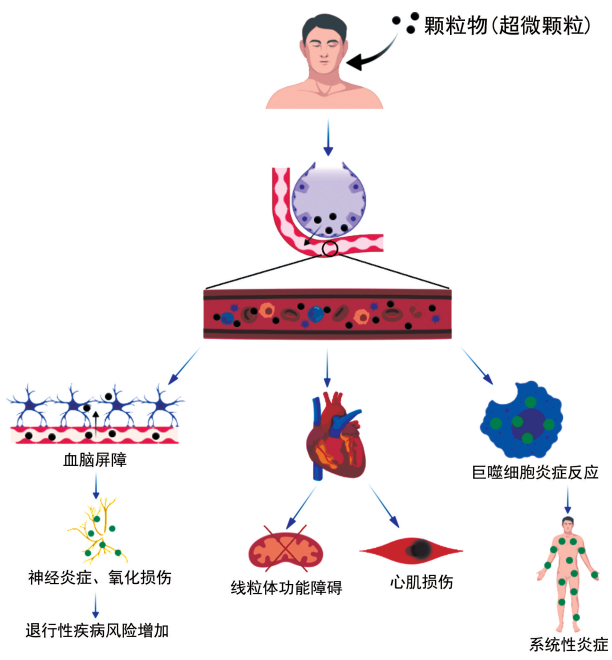

图 2 超微颗粒导致器官损伤途径

2.1 氧化应激

金属和化学物质附着在颗粒物上，通过产生促炎细胞因子和氧自由基/活性氧，引发炎症反应，进而导致氧化应激和脂质过氧化。过量的活性氧不仅会导致细胞器与细胞酶相互作用，还会对细胞膜、脂质等造成损伤[11]。在超微颗粒中也观察到类似效应，吸入超微颗粒后，肺部和心脏中的活性氧浓度迅速增加，导致氧化应激。在小鼠模型中，超微颗粒暴露增加了心肌中的氧化应激水平，尤其是在缺血-再灌注后，其会增加再灌注心肌中的中性粒细胞数量并促进活性氧的生成[15]。

一项涉及 2 035 例参与者的研究显示，颗粒物与氧化应激生物标志物之间存在正相关[16]。氧化应激水平的增加会诱导基质金属蛋白酶（matrix metalloproteinase，MMPs）激活，降低组织中 MMPs 抑制剂的水平，使得动脉粥样硬化斑块中的基质变性、破裂，从而增加心肌梗死风险[17]。暴露于高渗透性的超微颗粒中，可能会抑制 HDL-C 的抗炎潜能，并引发更强烈的氧化应激反应；脂质过氧化会促进促炎醛（即丙二醛）的产生，加速泡沫细胞的形成和动脉粥样硬化斑块的进展，最终增加心肌梗死发生风险[18]。

2.2 钙离子失衡和线粒体功能紊乱

细颗粒物通过影响钙离子调控和线粒体功能，导致心脏功能受损[19]。众所周知，钙离子在调节心肌细胞收缩强度和兴奋-收缩耦联中起着重要作用，钙循环异常，就会导致心脏收缩力的改变。有研究指出，暴露于颗粒物会抑制钙离子依赖的 ATP 酶并降低 ATP 水平，进而影响心肌细胞内钙离子浓度及钙离子调节蛋白功能，如肌浆网钙离子 ATP 酶、雷诺定受体 2 和钙调蛋白依赖性蛋白激酶Ⅱ，这些变化会导致心肌细胞电位不稳定，诱发心律失常等[20-22]。

附着在颗粒物表面的化学物质会对线粒体过渡孔（mitochondrial transition pore，MTP）的通透性产生影响，导致线粒体严重损伤，最终引起心脏功能障碍。钙离子水平升高会开放 MTP，而长期（不可逆）的开放会抑制 ATP 的产生并诱导线粒体的凋亡和坏死[23]。有研究表明，细颗粒物暴露会损伤心脏线粒体呼吸功能，增加线粒体超氧化物生成等，同时 ATP 合成不足会使心肌细胞损伤与坏死，心肌细胞大量坏死会导致心脏功能降低，使得心肌梗死面积扩大和心力衰竭发生[24]。

颗粒物中的化学和金属成分都是诱导心脏线粒体功能障碍的病因。而颗粒物（特别是超微颗粒）中的化学成分（如多环芳烃）通过影响线粒体功能，导致氧化应激、细胞凋亡和炎症反应，进而引发心肌梗死[25]。研究表明，超微颗粒中富含铁等金属，这些金属成分能够通过 Fenton 反应产生活性氧并积累在心

脏细胞的线粒体中，从而导致线粒体功能障碍[26]。有亚细胞分析研究指出，暴露于细颗粒物会影响线粒体的生物能量学，降低线粒体生物合成关键调节因子的表达[12]，由此进一步降低线粒体的功能。

2.3 ANS

有研究指出，暴露于细颗粒物会对心脏 ANS 产生影响[27]。心率变异度（heart rate variability，HRV）反映了心跳的不规则性并提示 ANS 的工作状态，HRV 越高，表示 ANS 状态越好。有研究以 39 例既往有心肌梗死史的患者作为研究对象，通过测量 24 h 内颗粒物暴露量，分析 24 h 心电图下的 HRV，结果显示 ANS 失调与超微颗粒暴露有关[28]。有文献指出，暴露于颗粒物会降低迷走神经张力，从而导致 HRV 降低[29]，表明心脏适应能力降低。同时，颗粒物会通过刺激肺上皮细胞中的神经元，改变 ANS 对血管的作用，最终改变 HRV[30]。同时，细颗粒物还会导致交感及副交感神经失衡，其中交感神经过度激活，副交感神经兴奋被抑制，最终降低 HRV[31]，提示心脏自主功能障碍[32]。同时，颗粒物对心脏 ANS 平衡的不良影响还反映在其对调压反应性和调节血管张力上，这一失衡将导致血压的升高[33]。

2.4 血管功能障碍

颗粒物可通过增加氧化应激、降低表达内皮型一氧化氮合酶和激活局部血管紧张素系统，诱导内皮细胞早衰从而导致血管功能障碍[34]。当内皮细胞受损后，斑块形成风险及心肌梗死风险随之增加。

内皮祖细胞（endothelial progenitor cells，EPCs）被认为是维持内皮细胞健康和稳定的细胞[35]。血管受损后，EPCs 会通过分泌促血管生成因子刺激现有内皮细胞增殖迁移，这有助于新生血管形成和血流运送重建[36]。由于血管内皮生长因子（vascular endothelial growth factor，VEGF）的通路被颗粒物抑制，阻止了 EPCs 从骨髓中动员，影响血管修复[37]。颗粒物暴露还会减少外周血中的 EPCs，进而影响血管修复能力[38]。据报道，在小鼠模型中，急性吸入超微颗粒同样会导致内皮损伤，引发 EPCs 的动员和功能受损[39]，表明超微颗粒可能通过影响内皮修复机制，加剧 CVD 风险。另有研究发现，淋巴细胞和粒细胞中的活性氧产生与早/晚期 EPCs 水平降低有关，表明超微颗粒可能通过氧化应激导致 EPCs 变化[40]。此外，活性氧可通过增加氧化应激、炎症反应及内质网的应激和自噬来增加血管钙化，从而导致动脉粥样硬化疾病的发生[41]。一项纵向研究指出，短期超微颗粒暴露会增加动脉僵硬程度[42]。

血管平滑肌细胞（vascular smooth muscle cell，VSMC）是动脉中膜层的主要细胞，其向内层的迁移和增殖被认为是内膜增生和斑块形成的重要原因[43]。有研究指出，多环芳烃通过 2 种机制影响 VSMC 的迁移；由于 MMPs 能够降解细胞外基质，所以多环芳烃通过提高 MMPs 的表达及活性来促进 VSMC 的迁移；多环芳烃通过激活黏着斑激酶和肉瘤病毒蛋白等通路，促进了黏着斑复合物的形成和细胞骨架的重组，增强了 VSMC 的迁移能力[44]，并最终导致心肌梗死风险增加。

内皮素-1（endothelin-1，ET-1）由内皮细胞产生，具有较强的血管收缩能力。试验表明，暴露于超微颗粒会增加血浆中的 ET-1[45]，这可能是空气污染诱发 CVD 发生的潜在机制。有研究表明，抑制 VEGF 受体会刺激细胞外信号调节激酶通路，增加内皮素前体原-1 的表达，同时也抑制蛋白激酶 B 通路并减少一氧化氮的产生[46]。还有研究表明，墨西哥儿童暴露于高浓度空气污染（包括超微颗粒）后，血浆中 ET-1 水平升高且与暴露时间呈正相关[47]。动物实验表明，暴露于超微颗粒会抑制内皮依赖性舒张[48]，血管反应性的改变会影响缺血组织的恢复。COZZI 等[15]研究结果显示，乙酰胆碱在 1、10 和 100 μmol/L 剂量下诱导的血管舒张程度明显受损。

2.5 炎症反应

颗粒物（尤其是细颗粒物和超微颗粒）沉积在肺部后，会激活肺泡巨噬细胞和其他免疫细胞，引发局部炎症反应。这种炎症反应主要表现为促炎细胞因子释放[49]。颗粒物可通过激活核因子-κB 通路，增加下游炎症细胞因子 IL-1β 和 IL-6 等的表达[50]。暴露于细颗粒物可导致野生型小鼠巨噬细胞炎症细胞因子标志物 IL-1 和环氧化酶-2 的表达水平明显提高[51]。炎症细胞因子会从肺泡细胞进入气道分泌物和血液中，诱发全身炎症反应[52]。小鼠实验表明，颗粒物通过激活肺泡的巨噬细胞释放促炎细胞因子引发全身炎症反应，加剧心肌梗死的炎症过程和心肌损伤；同时，沉积在血管内皮的颗粒物会增加局部氧化应激和炎症反应，致使斑块不稳定性增加[53]。暴露于颗粒物会诱导促炎基因的 mRNA 表达及炎症小体相关结构蛋白过表达[54]，使得心肌细胞中的炎症水平进一步升高。另有研究指出，肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）在细颗粒物诱导的心脏损伤中发挥了关键作用，抑制 TNF-α 可以恢复线粒体功能和心脏收缩功能，该研究支持炎症反应在细颗粒物诱导心脏损伤中的重要作用[55]。暴露于颗粒物会导致全身炎症的发生并最终使得心肌梗死的发生率增加[56]。

3 未解决问题

上述机制均被认为是解释本研究关注问题的潜在机制。证据支持最多的是氧化应激机制，其次是炎症反应机制。以上 2 种机制均有人体试验和动物实

验支持，而后者支持斑块形成风险的增加，间接展示了其诱发心肌梗死的证据。血管功能障碍机制缺乏人体试验；ANS 机制的途径尚未完全阐明；钙离子失衡机制仅通过动物实验（小鼠）证明颗粒物会降低心脏功能。

既往研究发现，暴露于颗粒物会提高炎症标志物水平[57]，本综述为这一观点提供了更多依据。但有研究认为颗粒物可能通过氧化应激和炎症细胞因子导致内皮功能障碍[58]，这一观点与本文阐述的机制略有不同，仍待进一步研究。

颗粒物为混合物，其成分十分复杂，意味着机制同样复杂。在未来研究方向上，血管功能障碍、钙离子失衡和 ANS 机制都需要从不同方面进行更深入的研究。前两者需要更多人体试验，而 ANS 机制则需进一步探究 ANS 与 HRV、HRV 与心肌梗死的相关性。

颗粒物已受到社会重视，通过环境保护措施，我国的细颗粒物水平已得到明显改善，但是以柴油尾气为主的超微颗粒的危害仍然缺乏大众重视。虽然颗粒物相关的氧化应激和炎症反应的机制已经被证实，但需要更多研究关注超微颗粒的机制。然而，目前超微颗粒研究受到仪器价格昂贵、标准化测量方法缺乏的限制[59]，有待学者研究出更合适的仪器及测量方法。

此外，如何降低高危人群发生心肌梗死风险也值得进一步研究。有研究认为，较低的温度会促进超微颗粒的形成[60]，因此高危人群在冬季应避免不必要的外出。对于既往有心肌梗死或其他 CVD 的患者，定期复查对于及早发现疾病变化并进行干预至关重要。对于普通人群，则建议补充 omega-3 脂肪酸和维生素 B 以减少颗粒物对心血管系统的影响，或是佩戴口罩来减少超微颗粒的吸入[61]。这些措施可在较大程度上降低由颗粒物（包括超微颗粒）引起的心肌梗死风险。

4 小　结

氧化应激和炎症反应是目前解释颗粒物暴露下诱发心肌梗死最合理的 2 种机制，所涉及的通路在一定程度上已得到明确研究，这为未来该类疾病的治疗和预防提供了方向和支持。而血管功能障碍、钙离子失衡和 ANS 机制则需更多研究，临床也可以基于上述机制制订治疗或预防策略。

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