·综　述·

二十碳五烯酸防治心血管疾病的进展

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摘要：研究显示二十碳五烯酸(EPA)可通过多种机制抑制动脉粥样硬化的发生发展，在对抗动脉粥样硬化、降低三酰甘油等方面的作用为治疗动脉粥样硬化性心血管疾病(ASCVD)提供了新的选择，本文对该方向的研究进展进行综述。

关键词：二十碳五烯酸；心血管疾病；动脉粥样硬化；三酰甘油
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ω-3 多不饱和脂肪酸(polyunsaturated fatty acids, PUFAs)的主要成分是二十碳五烯酸(eicosapentaenoic acid, EPA)和二十二碳六烯酸(docosahexaenoic acid, DHA)，近年 EPA 在心血管疾病领域独特的作用和机制引发关注。EPA 由 20 个碳原子和 5 个双键组成，多分布在血管内皮细胞，参与抑制氧化应激、炎症反应、泡沫细胞形成、血小板聚集及血栓形成等过程，能够降低三酰甘油、非高密度脂蛋白胆固醇、脂蛋白相关磷脂酶 A2(lipoprotein-associated phospholipase, Lp-PLA2)等。有研究表明，EPA 与他汀联用可改善心血管疾病预后，同时可作为指导预测心血管疾病风险的参考指标。本文聚焦 EPA 在心血管疾病防治领域的相关研究进展作一综述。

1　抗动脉粥样硬化机制

EPA 参与减少炎症因子生成、抑制氧化应激、调节血脂代谢、稳定斑块及抑制血栓形成等多个环节，了解 EPA 的作用机制有助于寻找防治动脉粥样硬化性心血管疾病的可能靶点。

1.1　抗炎和抑制氧化应激　EPA 可以通过降低 Lp-PLA2 水平从而减少氧化低密度脂蛋白磷脂水解为溶血磷脂酰胆碱和氧化的游离脂肪酸，下调细胞间黏附因子-1 及血管细胞黏附因子-1，抑制循环白细胞附着于血管内皮细胞，减轻血管炎症[1-2]；能够激活细胞表面 G 蛋白偶联受体 120 蛋白，抑制核因子(nuclear factor, NF)-κB 信号通路及诱导型一氧化氮合酶和基质金属蛋白酶的产生，降低血浆 IL-6 水平，同时降低促炎 CD14 基因表达，并增加抗炎过氧化物酶体增殖物激活受体 α(peroxisome proliferator-activated receptor-α, PPARα)、肿瘤坏死因子受体相关因子(TNF receptor associated factor, TRAF)3 基因表达[3]；EPA 亦降低正五聚蛋白 3(pentraxin 3, PTX-3)和单核细胞趋化蛋白 1(monocyte chemoattractant protein-1, MCP-1)的表达[4]；抑制环氧化酶-2 和 5-脂氧酶，削弱花生四烯酸衍生物的炎症作用；同时还可产生分解素 E3[5]，降低环磷腺苷效应元件结合蛋白 1(cAMP responsive element binding protein 1, CREB1)、缺氧诱导因子 1α(hypoxia-inducible factor 1-α, HIF-1α)及信号传导及转录激活因子 3(signal transducers and activators of transcription 3, STAT3)的表达[6]，发挥强大的抗炎效应。Mason[7]、Sherratt 等[8]研究发现，EPA 较强的亲脂性和电荷稳定性使其嵌入细胞膜，阻止自由基的传递，抑制高血糖诱导的脂质过氧化和胆固醇结构域的形成。Mason 等[9-10]分离了人体血浆中含有载脂蛋白 B(apolipoprotein B, ApoB)的脂蛋白，进行脂质氧化并加入 EPA 处理，证实 EPA 减少含有 ApoB 在内的脂蛋白颗粒氧化，抑制氧化应激，减轻内皮功能障碍。

1.2　调节脂代谢　Laguna-Fernandez 等[11]研究显示，EPA 通过下游分解素 E1 及 ERV1/ChemR23 受体信号通路参与降低极低密度脂蛋白胆固醇(very low-density lipoprotein cholesterol, VLDL-C)水平，减少巨噬细胞对氧化低密度脂蛋白的摄取。固醇调节元件结合蛋白-1(sterol regulatory element binding protein-1, SREBP-1)是血脂代谢稳态中重要的转录因子，EPA 能够抑制 SREBP-1 的活性从而减少三酰甘油的生成[12]；通过激活 PPAR-γ 增加内皮细胞肝素前脂蛋白脂酶(lipoprotein lipase, LPL)的活性，从而加快三酰甘油的清除[13-14]；通过增加脂肪酸 β-氧化、抑制酰基 CoA：1, 2-二酰甘油酰基转移酶、增强血浆 LPL 活性等途径降低脂蛋白残粒胆固醇(remnant-like particle cholesterol, RLP-C)水平[15]。Tanaka 等[16]发现 1.8 g/d EPA 可增强高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)的抗炎抗氧化效应及 HDL-C 介导的巨噬细胞胆固醇外排功能。Asztalos 等[17]在 121 名高血脂受试者中研究发现，连续 6 周服用 EPA 1.8 g/d 能够使 Lp-PLA2 降低 14.1%，从而参与降低心血管疾病的风险。

1.3　稳定动脉粥样斑块　Bargalló 等[18]应用气相色谱分析测定 161 名具有心血管疾病高危因素老年患者红细胞中的 EPA 含量，并应用增强 MRI 检测颈动脉斑块负荷及斑块稳定情况，发现 EPA 浓度与颈动脉斑块稳定性呈正相关。Konishi 等[19]将 60 名经皮冠状动脉介入治疗(PCI)的患者分为 EPA 干预

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组和对照组，应用光学频域成像分析冠状动脉斑块形态学特征，结果显示 EPA 组更少出现斑块破裂、斑块腐蚀、钙化结节、富含脂质的斑块，斑块更稳定。Watanabe 等[20]纳入 193 名 PCI 术后且服用匹伐他汀 4 mg/d 的患者，将其随机分为 EPA 组和对照组，随访 6～8 个月后运用集成反向散射血管内超声（integrated backscatter intravascular ultrasound，IB-IVUS）发现联合治疗组斑块体积显著缩小。

1.4　抑制血小板活化　Nomura 等[21]发现 2 型糖尿病合并血脂异常的患者服用 EPA 1.8 g/d 4 周后，血小板激活标记物（CD62P、CD63、膜联蛋白）和血小板衍生微粒（platelet-derived microparticles，PDMP）水平降低，表明 EPA 可抑制血小板活化。研究证实 EPA 可降低血小板微粒（MP）活性[22]，降低血小板黏附性[23]，提高红细胞变形能力并降低全血黏度[24]，从而抑制血小板聚集，影响血小板活化过程。

2　临床研究证据

2.1　治疗高三酰甘油血症　JELIS 研究[25]纳入 18 645 名总胆固醇大于 6.5 mmol/L 的受试者，随机分为 EPA 1.8 g/d+他汀组和他汀组，随访 5 年后发现 EPA 组三酰甘油水平降低更显著（9% *vs* 4%）。REDUCE-IT 研究[26]将 8 179 名服用他汀药物的受试者随机分为 EPA 4 g/d 和安慰剂组，随访 1 年后发现 EPA 组三酰甘油较对照组降低 19.7%，低密度脂蛋白胆固醇（LDL-C）较对照组降低 6.6%，HDL-C 无显著差异。Ballantyne 等[27]报道 ANCHOR 研究将 702 名正在接受他汀治疗的高三酰甘油血症（200～500 mg/dl）患者分组给予 EPA 4 g/d、2 g/d 及安慰剂，随访 12 周后，结果显示服用 EPA 的两组受试者不仅三酰甘油降低，总胆固醇、非 HDL-C、Lp-PLA2、ApoB、VLDL-C、LDL-C、RLP 等水平均降低，且 4 g/d 组三酰甘油（−21.5% *vs* −10.1%）、非 HDL-C（−13.6% *vs* −5.5%）水平降低更显著。

STRENGTH 研究是一项双盲随机对照的多中心研究，入选 13 078 位合并高三酰甘油血症、已服用他汀类药物的心血管高风险患者，比较服用 4 g/d EPA+DHA 与对照组（4 g/d 玉米油）1 年后的血脂指标变化，发现 EPA+DHA 组三酰甘油水平显著降低（−19% *vs* −0.9%），同时总胆固醇、非 HDL-C、ApoB、ApoCⅢ均降低，LDL-C、HDL-C 轻度升高[28]。一项纳入 22 项随机对照试验的荟萃分析显示 DHA 和 EPA 均可降低三酰甘油，DHA 较 EPA 作用更显著，但同时 DHA 升高 HDL-C 和 LDL-C[29]。综上，EPA 可降低血脂异常人群的三酰甘油水平，不增加 LDL-C 水平，4 g/d 剂量降低三酰甘油效果更显著。

2.2　对心血管疾病预后的影响　JELIS 研究随访 5 年后发现与单独使用他汀相比，冠心病二级预防亚组人群的主要冠脉事件发生率降低 19%。REDUCE-IT 研究中 70.7%为冠心病患者，随访的主要终点事件包括心血管死亡、非致命性心肌梗死、卒中、冠脉血运重建及不稳定性心绞痛等，中位随访 4.9 年后得出 EPA 组主要终点事件发生率降低 25%。上述研究亦揭示了 EPA 与他汀联合应用在二级预防领域的治疗价值。一项纳入 5 项随机临床试验的荟萃分析表明，与单独使用他汀相比，EPA 联合他汀治疗可降低 18%的主要不良心血管事件及 30% 的心肌梗死发生率[30]。但近期公布结果的 STRENGTH 研究未能进一步证实包含 EPA 在内的 ω-3 脂肪酸对心血管疾病结局的改善作用，中位随访 42 个月后发现两组患者的主要不良心血管事件无显著差异。因目前缺乏关于 DHA 单纯制剂对心血管疾病预后影响的大规模研究，尚不清楚 STRENGTH 研究未得出同 REDUCE-IT 研究一致心血管获益的结论是否可归因于 EPA 与 DHA 的比例。

2.3　指导预测心血管疾病风险　通过测量血液中红细胞 EPA 和 DHA 浓度计算出的 ω-3 指数[31-32]可用于预测冠心病死亡风险，当 ω-3 指数≥8%时，冠心病死亡率将降低一半以上，当 ω-3 指数≤4%时，心脏的保护作用甚微。Harris 等[33]纳入了 1 144 名急性心肌梗死患者进行研究，发现结合红细胞 EPA 水平能够提高 GRACE 评分对急性心肌梗死患者 2 年死亡率预测的准确性。Block 等[34]的动脉粥样硬化队列研究（MESA 队列，n=6 562）显示，血浆高 EPA 水平与低心力衰竭风险相关。Ninomiya 等[35]纳入 3 103 名 40 岁以上的研究对象并随访 5.1 年后发现，低血浆二十碳五烯酸/花生四烯酸（EPA/AA）比值与心血管疾病高风险相关，特别是与冠心病相关。Watanabe 等[36]通过对 577 名心衰患者的观察研究发现，EPA/AA 比值是心衰患者死亡率的独立预测因子。

3　心血管疾病指南推荐

2019 年 ESC/EAS 血脂异常管理指南中推荐，对三酰甘油水平在 1.5～5.6 mmol/L（135～499 mg/dl）、已经应用他汀类药物的患者，建议联合补充 EPA 2 g bid（Ⅱa，B）[37]。2019 年美国国家脂质协会的科学声明，推荐≥45 岁的动脉粥样硬化性心血管疾病患者或≥50 岁合并至少一项危险因素的糖尿病患者，若三酰甘油水平在 1.5～5.6 mmol/L（135～499 mg/dl）或者他汀类药物治疗已达最大耐受剂量，建议联合 EPA 治疗（ⅠB）[38]。2019 年 AHA 科学建议表明，不论是否与其他降脂药物联合应用，EPA+DHA 或 EPA 制剂 4 g/d 均可安全有效地降低三酰甘油水平（三酰甘油水平 500～2 000 mg/dl 患者降低≥30%，三酰甘油水平 200～499 mg/dl 患者降低 20%～30%）[39]。美国食品药品监督管理局（FDA）批准多种 EPA+DHA 或 EPA 制剂用于高三酰甘油血症的治疗，如 Omtryg（ω-3-酸乙酯），Vascepa（EPA），Epanova（EPA+DHA）等。

综上，EPA 有望成为合并高三酰甘油血症心血管疾病人群的联合治疗选择，但 EPA 对心血管的具体保护机制、EPA/DHA 配比或浓度与疗效的关系尚不明确，需大规模研究进一步探索。

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(上接第 1422 页)

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