抗炎类药物对射血分数保留性心力衰竭患者心外膜脂肪组织的影响

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【摘要】心外膜脂肪组织在心血管疾病中起着重要作用。近年来研究发现,慢性炎症或代谢紊乱可引起心外膜脂肪组织分泌脂肪因子及游离脂肪酸,进一步导致心功能障碍,最终加快心力衰竭的发展,尤其是射血分数保留性心力衰竭。临床研究证实抗炎类药物(如他汀类药物和抗细胞因子制剂)能降低心外膜脂肪组织厚度,改善炎症状态,有利于降低射血分数保留性心力衰竭患者的死亡风险,现就抗炎类药物对射血分数保留性心力衰竭患者心外膜脂肪组织的影响进行系统综述。

【关键词】抗炎类药物;心外膜脂肪组织;射血分数保留性心力衰竭
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Effects of Anti-Inflammatory Drugs on Epicardial Adipose Tissue in Patients with Heart Failure with Preserved Ejection Fraction

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【**Abstract**】Epicardial adipose tissue(EAT) plays an important role in cardiovascular disease. Recent studies have found that chronic inflammation or metabolic disorder can cause EAT to secrete adipokines and free fatty acids, further lead to cardiac dysfunction, and finally accelerate the development of heart failure, especially heart failure with preserved ejection fraction(HFpEF). Clinical studies have confirmed that anti-inflammatory drugs(statins and anti-cytokine agents) can reduce EAT thickness, improve the state of inflammation, and reduce the risk of death in patients with HFpEF. The effects of anti-inflammatory drugs on EAT in patients with HFpEF are systematically reviewed in this paper.

【**Key words**】Anti-inflammatory drugs; Epicardial adipose tissue; Heart failure with preserved ejection fraction

心力衰竭(心衰)是由多种原因导致心脏结构和/或功能的异常改变,使心室收缩和/或舒张功能发生障碍,从而引起的一组复杂的临床综合征。2016 年欧洲指南将心衰分为射血分数降低性心衰(heart failure with reduced ejection fraction, HFrEF)、射血分数保留性心衰(heart failure with preserved ejection fraction, HFpEF)和中间范围射血分数心衰[1]。在 60 岁以上的人群中,有 4.9% 被诊断为 HFpEF,因心衰住院的患者中超半数的患者被诊断为 HFpEF[2],而目前针对 HFpEF 的有效治疗尚未明确。在慢性炎症性疾病中(尤其是导致 HFpEF 的疾病),心外膜成为脂肪生成紊乱的场所,分泌促炎症脂肪细胞因子,引起心房和心室纤维化[3]。脂肪组织是一种复杂的内分泌器官,除了储存脂肪,脂肪组织能分泌多种脂肪因子,参与心脏的代谢和功能[4]。在过去的几十年里,心外膜脂肪组织(epicardial adipose tissue, EAT)因其解剖和功能特点在各种心血管疾病中得到广泛的研究,EAT 测量可作为评估心血管和代谢风险的潜在诊断工具[5],有望成为心衰、心房颤动和 2 型糖尿病患者炎症状态的标志物[6]。此外,通过减肥和药物治疗来改变 EAT 厚度对心血管疾病、糖尿病和代谢综合征具有治疗意义[7]。

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1　EAT 的解剖及特点

EAT 是位于心肌与心包脏层之间独特的内脏脂肪组织，主要位于房室沟及室间沟，覆盖大部分心脏血管，增加心脏代谢。EAT 和心肌之间无解剖边界，它们共享冠状动脉微循环，并为心肌提供脂肪酸作为能量来源[8]，EAT 可释放各种类型的脂肪因子，如脂联素、肾上腺髓质素、多种促炎细胞因子、肿瘤坏死因子-α 和白介素-1 等[9]，通过促炎和抗炎细胞因子的旁分泌作用局部调节心脏和脉管系统，从而在肥胖相关的炎症和动脉粥样硬化中发挥潜在作用[10]。此外，EAT 储存或释放游离脂肪酸以满足动脉壁和心肌的能量需求，从而避免脂毒性，当游离脂肪酸超载时（在肥胖和糖尿病患者中），β 氧化被过度激活，导致活性氧的产生和肌质网钙 ATP 酶的调节改变，这是舒张功能障碍、心肌纤维化和心肌细胞肥大的早期促成因素[11]。

2　EAT 与肥胖和 HFpEF

肥胖不仅是一种脂肪生成状态，而且是一种全身炎症性疾病。肥胖人群中最常见的心肌疾病为 HFpEF[12]，其主要的病理生理异常是心室扩张性下降，左室对血容量增加的反应能力受损。而限制心室扩张的主要机制是微循环障碍和心肌纤维化，纤维化的数量与心脏舒张、功能容量和结局密切相关[13]。肥胖会增加 EAT 的质量并导致心房电紊乱以及舒张充盈异常，从而使心衰风险增加[14]。Wu 等[15]试验表明 HFpEF 患者的 EAT 明显多于 HFrEF 患者和非心衰患者，而且 EAT 厚度与 HFpEF 患者的左室舒张功能障碍参数相关。肥胖是 HFpEF 的独立危险因素，脂毒性、炎症、线粒体功能障碍、内质网应激以及细胞凋亡等多种致病因素可能参与了肥胖诱导的 HFpEF[16]。一项关于接受/未接受减肥手术的肥胖患者心衰风险的研究[17]认为，通过减肥手术，除了体重大幅下降外，同时伴随 EAT 数量减少，全身炎症强度降低，心衰风险降低。除此之外，手术切除 EAT 能改善心室功能和结构[18]。然而与 HFrEF 患者相比，减轻体重的临床益处主要见于 HFpEF 患者[19-20]。

3　抗炎类药物对 EAT 的影响

HFpEF 与 HFrEF 具有不同的病理生理机制，故两类心衰的治疗不完全相同。神经激素拮抗剂对 HFrEF 的治疗有效，而对 HFpEF 患者效果欠佳。在 HFpEF 的高危人群中，促进心外膜脂肪积聚或炎症的药物可能导致心衰，改善 EAT 促炎状态的药物能降低心衰的风险，这表明，EAT 是全身炎症和代谢紊乱对心脏产生不利影响的传感器[21]，是治疗干预的重要手段。抗炎类药物（如他汀类药物和抗细胞因子制剂）可减少 EAT，改善炎症状态[22]。他汀类药物主要用于降低代谢性疾病（如血脂异常和 2 型糖尿病）患者动脉粥样硬化缺血事件的风险，抗细胞因子药物用于治疗全身性炎症性疾病（如类风湿性关节炎、牛皮癣和炎症性肠病）。

3.1　他汀类药物

他汀类药物的抗炎作用最初用于冠状动脉粥样硬化性疾病，现在也用于改善全身炎症性疾病以及脂肪代谢紊乱[22]。他汀类药物通过影响细胞结构、血管分布及炎症状态使 EAT 代谢活动降低[23]，进一步改善 EAT 的促炎状态，减轻心室舒张功能障碍和心肌纤维化[16]。研究发现，他汀类药物改善心外膜脂肪的炎症状态，可对大鼠的心脏重构产生有利影响[24]。Alexopoulos 等[25]的一项临床随机对照试验表明，大剂量的他汀类药物可减少合并高脂血症的绝经后女性的 EAT 质量。这一结果取决于他汀类药物的抗炎作用，与低密度脂蛋白胆固醇降低的程度无关。他汀类药物在治疗全身炎症性疾病的同时可降低心衰患者的 N 末端脑钠肽前体水平[26]，强化他汀类药物的治疗降低了新发心衰的风险[27]；他汀类药物还可降低确诊为 HFpEF 患者的死亡风险，包括非心血管死亡的发生[28-29]；然而在 HFrEF 患者中，他汀类药物对其发病率和死亡率无明显改善及益处[30]。虽然上述研究确定了他汀类药物对减轻 EAT 厚度以及对 HFpEF 患者的有利影响，但其直接作用还需进一步研究。

3.2　抗细胞因子药物

EAT 释放各种类型的脂肪因子，如肿瘤坏死因子-α、白介素-1β、白介素-6 和单核细胞趋化因子蛋白-1 等[31]，并通过血管分泌或旁分泌信号通道转移到动脉壁、管腔和心肌细胞中产生心肌脂毒性，进一步导致心肌功能障碍或心衰[9]。临床研究证实，全身炎症标志物与 HFpEF 和慢性炎症性疾病患者的心脏功能和预后不良相关[32]。近年来，多个文献报道了抗细胞因子药物能改善心功能。阿那白质素（白介素-1 阻滞剂）治疗能显著降低类风湿性关节炎（一种白介素-1 相关疾病）患者的全身炎症反应并改善其心脏舒张功能[32]。白介素-1β 抑制剂卡纳单抗可降低炎性生物标志物和因心衰住院的风险[33]。Wolfe 等[34]的研究表明，肿瘤坏死因子-α 拮抗剂能有效地降低类风湿性关节炎患者的心衰风险。因而，抗细胞因子药物可能会在预防易患和已患 HFpEF 患者病情发生和发展方面具有重要作用[22]。但关于抗细胞因子的临床试验仍较少，而且其价格昂贵，限制了其在临床的广泛使用。

4　结论与展望

EAT 因其解剖和功能特点在 HFpEF 的发生和发展中发挥重要作用。目前研究表明改善 EAT 的结构

和功能是治疗 HFpEF 的重要靶点,其中抗炎类药物治疗对减少 EAT 质量有较好的疗效,并通过改善其炎症状态,降低新发心衰风险及心衰患者死亡率,临床上如何更准确地评价抗炎类药物对 HFpEF 患者 EAT 的影响,尚需多中心和大规模的临床试验以及临床分析的支持。

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