

· 心房颤动专题研究 ·

胰岛素抵抗与心房颤动

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【摘要】 心房颤动 (AF) 是目前临床上最常见的心律失常类型。胰岛素抵抗 (IR) 可通过引起心肌组织氧化应激及炎症反应等多种途径导致心房重构, 从而参与AF的发生发展过程。三酰甘油葡萄糖 (TyG) 指数作为评估IR的工具, 也可以预测AF的发病风险及预后。本文主要综述了IR导致AF的机制、IR评估工具对AF的预测价值及治疗IR对AF的影响, 以期对AF的早期诊断、及时治疗提供参考依据。

【关键词】 心房颤动; 胰岛素抵抗; 三酰甘油葡萄糖指数; 预后; 综述

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【Abstract】 Atrial fibrillation (AF) is the most common type of arrhythmia in clinical practice. Insulin resistance (IR) can lead to atrial remodeling by causing oxidative stress and inflammatory response in myocardial tissue, thus participating in the occurrence and development of AF. Triglyceride glucose (TyG) index, as a tool to evaluate IR, can also predict the risk and prognosis of AF. This article mainly reviews the mechanism of IR-induced AF, the predictive value of IR assessment tools for AF and the effect of IR treatment on AF, in order to provide reference for early diagnosis and timely treatment of AF.

【Key words】 Atrial fibrillation; Insulin resistance; Triglyceride-glucose index; Prognosis; Reviews

心房颤动 (atrial fibrillation, AF) 是目前临床上最常见的心律失常类型, 近年随着我国人口老龄化进程加剧, AF发病率不断升高, 其对人们生命健康的危害亦进一步加重^[1]。因此, 寻找有效的风险预测因子和干预措施是AF治疗的重点。胰岛素抵抗 (insulin resistance, IR) 是机体对胰岛素作用的敏感性和反应性降低的病理状态^[2], 其主要表现为糖、脂、能量代谢异常。有动物实验和临床研究表明, IR可通过引起心肌组织氧化应激及炎症反应等多种途径而导致心房重构, 从而参与AF的发生发展过程^[3-5]。三酰甘油葡萄糖 (triglyceride-glucose, TyG) 指数作为评估IR的工具^[6], 也可以预测AF的发病风险及预后。本文主要综述了IR导致AF的机制、IR评估工具对AF的预测价值及治疗IR对AF的影响, 以期对AF的早期诊断、及时治疗提供参考依据。

1 IR导致AF的机制

1.1 IR导致心房电重构 心房电重构指心房有效不应期 (atrial effective refractory period, AERP) 和动作电位时程

(action potential duration, APD) 进行性缩短、动作电位传导速度减慢、局部阻滞和心房肌不应期离散度增加等, 是AF发展和维持的重要因素^[7]。研究表明, 1型糖尿病大鼠模型伴有糖耐量受损, 对胰岛素反应减弱, 心房肌细胞钙离子调节功能受损, 心房肌细胞APD明显延长^[8]。在糖尿病大鼠模型中, 细胞瞬时外向钾电流和L型钙通道电流密度不一致, 同时心房肌细胞多种离子通道编码蛋白表达水平明显降低, 离子通道电流传导减弱, 进而加剧了心房电重构程度, 增加了AF易感性^[9]。IR可导致线粒体产生大量活性氧 (reactive oxygen species, ROS)^[10], ROS又可直接作用于心房离子通道, 尤其是细胞内钙调节蛋白的氧化修饰, 导致细胞内钙超载及延迟后除极, 进而引起心房电重构^[3]。心脏自主神经重构在AF启动、维持和预后中起重要作用, 其中迷走神经兴奋可延长心肌细胞有效不应期, 增加不应期的离散度, 提高心房肌细胞对AF的易感性; 而交感神经兴奋可使心肌细胞自律性增加, 心肌细胞触发活动明显增多, 二者失衡可导致心房电重构^[11]。IR可导致心脏自主神经功能紊乱, 进而加重心房电重构, 增加AF发生概率^[12]。

1.2 IR导致心房结构重构 心房结构重构是AF的中心环节, 心房纤维化是其主要表现^[13]。IR可通过增强氧化应激而使促纤维基因表达上调, 成纤维细胞增殖, 从而加重心房纤维化及增加AF发生率^[14]。既往研究表明, 二甲双胍可通过减轻细胞内的氧化应激而防止细胞结构快速重构, 进而降低糖

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尿病患者AF发生风险^[4]。转化生长因子 $\beta 1$ (transforming growth factor beta 1, TGF- $\beta 1$)是心房纤维化的主要通路之一^[15], IR大鼠模型心房TGF- $\beta 1$ 表达升高, 而吡格列酮作为胰岛素增敏剂, 可通过抑制TGF- $\beta 1$ 表达而减轻心房纤维化, 进而降低AF发生率^[16], 提示IR通过引起心房结构重构而参与AF的发生。

研究表明, IR可导致机体多种炎性因子水平升高, 如促炎因子TNF- α 、IL-6及C反应蛋白(C-reactive protein, CRP)等, 进而引起心房肌组织被炎性细胞浸润^[17-18], 促进心房纤维化和心脏舒张功能障碍, 加重心房重构, 维持AF的持续性。研究表明, CRP水平与左心房内径呈正相关, 持续性AF患者CRP水平明显高于阵发性AF患者^[19]。而长期炎症反应可进一步降低机体对胰岛素的敏感性, 加重IR; 同时, IR可导致脂质代谢紊乱、内脏脂肪沉积和心外膜脂肪组织浸润, 引起异位病灶和异质性传导, 形成折返激动^[20], 从而促进AF的发生。上述因素相互作用, 可加重心房结构重构, 进而促进AF的发生。

2 TyG指数

目前, 诊断IR的“金标准”是正常血糖胰岛素钳夹试验, 由于其为侵入性试验且价格昂贵, 故未能广泛用于临床实践^[21]。目前, 临床上应用较广泛的评估IR程度的工具是稳态模型-胰岛素抵抗(homeostasis model assessment insulin resistance, HOMA-IR)指数, 但其对接受胰岛素治疗或胰岛 β 细胞功能完全丧失的患者的评估价值有限^[22]。2008年, SIMENTAL-MENDÍA等^[23]在健康人群的大型横断面研究中, 首次提出TyG指数较HOMA-IR指数能更好地评估IR。随后GUERRERO-ROMERO等^[24]研究也证实, TyG指数是评估IR的最佳工具, 与正常血糖胰岛素钳夹试验相比, TyG指数诊断IR的灵敏度为96.5%、特异度为85.0%。同时, 根据空腹血糖(fasting plasma glucose, FPG)和三酰甘油(triglyceride, TG)计算的TyG指数计算方便, 可重复检测。

3 IR评估工具对AF的预测价值

研究证实, IR是AF的独立危险因素^[25], IR患者易出现多种代谢紊乱, 如高血糖、血脂异常和高血压等, 而代谢紊乱与AF的发生相关^[26]。SHIGEMATSU等^[27]研究结果显示, 伴有AF的非糖尿病肥胖型心肌病患者中IR占比明显高于伴有窦性心律的非糖尿病肥胖型心肌病患者, 提示IR可能是介导AF发生的潜在机制。LEE等^[28]通过对8 175名社区人群随访发现, HOMA-IR指数 ≥ 1.4 的人群AF发生率较HOMA-IR指数 < 1.4 的人群增加了约60%, 且调整肥胖、高血压、血管疾病、心力衰竭等混杂因素后, HOMA-IR指数 ≥ 1.4 的人群AF发生率仍明显高于HOMA-IR指数 < 1.4 的人群。2016年, SÁNCHEZ-ÍÑIGO等^[29]首次提出, TyG指数对心血管疾病具有一定诊断价值[AUC=0.708, 95%CI (0.68, 0.73)], $P=0.014$ 。之后有研究表明, TyG指数对冠心病、高血压、心力衰竭的发生和预后具有一定预测价值^[30-34]。SHI等^[35]进行的横断面研究结果显示, TyG指数与糖尿病患者发生AF有关, 而将TyG指数引入常见的心血管疾病危险因素中, 可提高AF的检出率。上述研究提示, TyG指数在预测AF发生风险

方面具有潜在的应用价值。

《2020欧洲心脏病协会(ESC)心房颤动诊断与管理指南》推荐, 导管消融治疗是阵发性AF和持续性AF的一线治疗方案^[36]。但导管消融治疗术后AF复发率高达20%~50%^[37], 故寻找并干预影响AF患者维持窦性心律的危险因素至关重要。日本一项研究纳入了114例行肺静脉隔离术(pulmonary vein isolation, PVI)的阵发性AF患者, 术后对其随访(357 $\pm$ 170)d, 结果显示, IR组患者AF复发率明显高于非IR组, 多元Cox回归分析结果显示, IR是阵发性AF患者PVI后复发的独立影响因素($HR=1.287$, $P=0.004$)^[25]。TANG等^[38]进行的一项回顾性研究表明, 在非糖尿病患者中, TyG指数升高与射频消融术后晚期AF复发独立相关; 此外, TyG指数与AF预后风险评分量表评分(如APPLE评分、DR-FLASH评分和CHA₂DS₂-VASc评分)呈正相关。同样的, WANG等^[39]的一项观察性研究共纳入232例非糖尿病AF患者, 结果显示, HOMA-IR指数高是非糖尿病AF患者射频消融术后AF复发的独立危险因素。上述研究提示, IR与射频消融术后AF复发相关, IR评估工具对AF复发具有一定预测价值。

4 治疗IR对AF的影响

IR作为2型糖尿病及代谢综合征的病理生理学基础^[26], 与AF的发生发展及预后明显相关, 故消融治疗前治疗IR有望减少AF复发率。目前, IR常规治疗方法主要有生活方式干预和药物治疗^[40]。噻唑烷二酮类(thiazolidinedione, TZD)是目前最常用的胰岛素增敏剂, 其可以抑制单核细胞趋化蛋白1介导的炎性纤维化过程及线粒体和血清中的氧化应激反应, 进而改善IR^[41-43]。一项Meta分析结果显示, 在接受TZD治疗的糖尿病患者中, 新发AF及AF复发风险约降低30%^[44]。由于TZD的不良反应为水钠潴留和脂肪沉积^[41], 可造成水肿、心脏容量负荷增加和体质量增加, 故在AF合并心功能不全的患者中需谨慎使用TZD。胰高血糖素样肽1受体激动剂(glucagon-like peptide-1 receptor agonists, GLP-1RA)可促进脂肪细胞对葡萄糖的摄取, 提高胰岛素敏感性^[45]。GASPARI等^[46]研究表明, 利拉鲁肽(liraglutide, LIR)在多种病理状态下均能减轻心肌间质纤维化; NAKAMURA等^[47]研究表明, LIR能抑制犬AF模型的电生理变化, 降低AF发生率。一项Meta分析结果显示, 与安慰剂相比, GLP-1RA可降低AF/心房扑动发生风险^[48]。但目前尚无研究证实GLP-1RA对射频消融术后AF复发有影响, 而鉴于其对心房重构的抑制作用, 或可成为AF治疗领域的研究重点。

钠-葡萄糖协同转运蛋白2抑制剂(sodium-dependent glucose transporter 2 inhibitors, SGLT2i)是目前关注度较高的新型口服降糖药, 其具有降糖外的心肾保护作用^[49]。SGLT2i主要通过抑制肾脏近端小管钠-葡萄糖协同转运蛋白2受体而降低肾糖阈, 促进尿葡萄糖排泄, 减少肾脏近端小管对葡萄糖和钠的重吸收, 从而达到降低血糖的目的, 同时具有减轻体质量和降低血压的作用^[50]。此外, SGLT2i还可以通过改善IR而对AF发挥一定治疗作用, 其相关机制主要如下: (1) SGLT2i可能改善心房线粒体功能, 减轻ROS导致的氧化应激, 从而改善心肌结构、功能及减轻心肌纤维化程

度,降低AF发生风险^[51-52]。(2)SGLT2i通过抑制心肌细胞上的离子通道转运功能而增加细胞对Ca²⁺和Na⁺的转运,降低细胞内Ca²⁺水平,抑制AF致病因子如钙/钙调蛋白依赖性蛋白激酶2等,增加ATP合成,从而延缓心房重构^[8]。(3)心外膜脂肪组织可分泌多种促炎物质,其厚度增加与左心房重构、AF发生和AF严重程度有关^[20]。SGLT2i具有减轻体质量的作用,其可通过调节脂质代谢而改善IR,减轻心外膜脂肪组织堆积,进而达到减轻心房重构和减少AF发生的目的。

近年大量临床研究证实,SGLT2i具有明确的心血管和肾脏获益,尤其适用于合并心力衰竭或慢性肾脏病的糖尿病患者,且可以降低AF/心房扑动发生风险^[53-56]。DECLARE-TIMI 58研究^[53]的亚组分析结果显示,达格列净可有效降低2型糖尿病患者AF/心房扑动发生率。有两项Meta分析结果显示,SGLT2i可有效降低AF发生风险^[54-55]。BUTT等^[56]研究表明,SGLT2i可降低射血分数保留的心力衰竭合并AF患者的心血管事件发生率,且与AF分类无关。目前,SGLT2i已被我国临床指南推荐作为治疗心力衰竭的新四联药物之一^[49],随着更多基础及临床证据的公布,SGLT2i有望成为治疗AF及改善AF预后的另一方案。

5 小结

综上,IR可通过增强炎症和氧化应激、抑制细胞离子通道活性、增加心外膜脂肪堆积等途径而导致心房重构,这与AF的发生发展及消融治疗术后AF复发密切相关。IR评估工具TyG指数和HOMA-IR指数对AF发生及消融治疗术后AF复发具有一定预测作用。而改善IR的药物TZD和GLP-1RA对降低AF发生率及消融治疗术后AF复发率具有积极作用。新型口服降糖药SGLT2i可通过抗炎、抑制氧化应激反应、调节脂质代谢等途径而改善IR,减少心房重构。对于非糖尿病AF患者,临床医生可通过TyG指数判断IR情况以指导SGLT2i的应用,从而利于临床医生综合管理AF患者。

作者贡献:牛毅菲进行文章的构思与设计、文献/资料收集,撰写、修订论文;黄琼进行文章的可行性分析;贺宇进行文献/资料收集;袁义强负责文章的质量控制及审校,并对文章整体负责、监督管理。

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