

· 综述 ·

心脏术后新发糖尿病的危险因素：进展与思考

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【摘要】心脏术后新发糖尿病是心脏手术常见的并发症之一，可增加术后死亡和排异事件的发生风险。对心脏术后新发糖尿病的早期发现和积极管理是促进心脏手术患者临床获益的重要内容。本文通过对冠脉血运重建术和心脏移植术两种重要心脏手术类型术后新发糖尿病的危险因素作一综述，以期为心脏术后新发糖尿病的早期综合化管理提供参考。

【关键词】糖尿病；冠脉血运重建术；心脏移植术；危险因素

Risk factors for new-onset diabetes after cardiac surgery: progress and consideration

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【Abstract】New-onset diabetes is one of the most common complications after cardiac surgery, which can lead to increased mortality and rejection events. Early detection and active management of new-onset diabetes after cardiac surgery are important contents to promote the clinical benefits of patients undergoing cardiac surgery. Therefore, this paper reviews the risk factors for new-onset diabetes after two important types of cardiac surgery coronary revascularization and heart transplantation, in order to provide references for the early and comprehensive management of new-onset diabetes after cardiac surgery.

【Keywords】Diabetes mellitus; Coronary revascularization; Heart transplantation; Risk factors

糖尿病是心脏手术的重要并发症之一，其患病率可高达 30%~40%^[1]。随着心脏手术的广泛开展，心脏术后新发糖尿病也逐渐引起关注。研究显示，冠脉血运重建术后新发糖尿病患病率为 11.8%^[2]，心脏移植术后新发糖尿病（new-

onset diabetes mellitus after heart transplantation, NODAT）的患病率达 20%~30%^[3]。心脏术后新发糖尿病可致患者术后死亡率、排异事件及再移植风险显著增加，导致不良预后，坚持早诊早治具有重要意义^[4-6]。

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目前临床常见的心脏手术包括经皮冠脉介入术 (percutaneous coronary intervention, PCI)、冠状动脉旁路移植术 (coronary artery bypass graft, CABG)、心脏移植术等, 其中 PCI 和 CABG 等冠脉血运重建术是解决心脏血管解剖学狭窄、恢复心肌再灌注最常用的治疗手段, 心脏移植术是治疗终末期心脏功能衰竭、延长生存时间唯一有效的治疗方法。

近年来研究发现心脏术后新发糖尿病的发生与人口学因素, 如年龄、性别、体重指数 (body mass index, BMI)、遗传因素 (糖尿病家族史、种族、基因)、糖脂代谢状态及用药因素 (他汀类药物、免疫抑制剂) 等多个方面密切相关 (图 1), 本文通过对冠脉血运重建术和心脏移植术这两种重要心脏手术类型术后新发糖尿病危险因素进行较为系统的整理和分析, 为临床早期有效识别心脏术后新发糖尿病高风险人群, 继而对可控危险因素进行早期干预以改善临床预后提供参考。

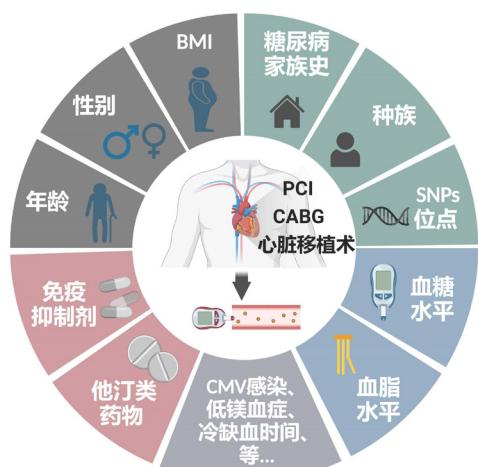


图1 心脏术后新发糖尿病危险因素

Figure 1. Risk factors for new-onset diabetes after cardiac surgery

注: PCI: 经皮冠状动脉介入治疗术; CABG: 冠状动脉旁路移植术; BMI: 体重指数; SNPs: 单核苷酸多态性; CMV: 巨细胞病毒

1 心脏移植术后新发糖尿病的危险因素

1.1 人口学因素

年龄、性别和 BMI 是影响患者发生 NODAT 的常规人口学因素。研究表明, 50 岁以上、男性、高 BMI 的患者发生 NODAT 的风险更高 [5,7-9]。与 $BMI < 25 \text{ kg/m}^2$ 患者相比, $BMI \geq 25 \text{ kg/m}^2$ 的患者 NODAT 相对风险增加 55%, $BMI \geq 30 \text{ kg/m}^2$ 的患者 NODAT 相对风险更是增加 90% [7]。

1.2 糖脂代谢状态

血糖水平与 NODAT 的发生密切相关。多项研究显示, 术前高空腹血糖 (fasting plasma glucose, FPG) 可致 NODAT 发病风险升高 5 倍以上 [9-10]。Munshi 等对 109 例行心脏移植术的患者进行随访, 结果发现移植术后平均血糖水平与 NODAT 风险升高显著相关 [11]。因此, 无论是基线血糖水平还是术后血糖水平均与心脏移植术后新发糖尿病的风险增加密切相关。

上述因素与糖尿病的发病危险因素相同, 据此推测其机制可能也存在相似性 [6,10], 如增龄可致胰岛 β 细胞发生退行性改变, 肥胖会造成外周组织胰岛素代谢障碍以及基线血糖水平较高者更易按照“正常血糖状态 – 血糖稳定机制损害 – 糖尿病”的发病过程进展为糖尿病等。因此, 与糖尿病的临床诊疗相同, 积极控制血糖、血脂和体重等常规风险因素的达标对心脏术后患者至关重要。

1.3 用药因素

免疫抑制剂是心脏移植术后的常规用药, 目前已被公认是 NODAT 的主要危险因素之一。大量研究显示, 钙调神经磷酸酶抑制剂 (calcineurin inhibitors, CNIs) 环孢素和他克莫司、哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR) 抑制剂雷帕霉素的使用均可不同程度的增加 NODAT 发病率, 且他克莫司相关的 NODAT 风险更高 [4,7,12]。他克莫司血药浓度 $\geq 110 \text{ ng} \cdot \text{mL}^{-1}$ ($\text{mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) 也被认为是 NODAT 发生的独立危险因素 [13], 其作用机制与他克莫司可靶向胰岛、肾脏、肝脏等多部位, 参与钙调神经磷酸酶 / 活化 T 细胞核因子 (NFAT)、mTOR 及免疫相关等多条通路从而影响葡萄糖代谢有关 [14]。类固醇激素通过降低胰岛素受体数量、减少外周组织的葡萄糖摄取, 产生胰岛素抵抗, 亦可导致 NODAT 的发生 [4,10,15]。

1.4 遗传因素

糖尿病已被证实是多因素、多基因作用的疾病, 具有遗传易感性。心脏术后新发糖尿病也与遗传密切相关, 多项研究均表明糖尿病家族史和种族皆是 NODAT 的危险因素 [7,9-10,16], 有糖尿病家族史和非白种人种族的患者 NODAT 的风险更高, 种族差异可能与不同种族人群间对于免疫抑制剂的药物代谢动力学不同有关 [17]。在基因研究方面, 单核苷酸多态性 (single-nucleotide

polymorphisms, SNPs) 位点也被发现在 NODAT 中起着重要作用, 免疫及炎症相关的 CC 趋化因子配体 5 (chemokine ligand 5, CCL5) rs2280789 等位基因是 NODAT 的独立危险因素^[18]。

1.5 其他

除上述危险因素外, 近年来在 NODAT 的研究中发现巨细胞病毒 (CMV) 感染^[8]、移植术后低镁血症^[19]、冷缺血时间延长^[10]等与 NODAT 发生也存在相关性。Zielinska 等的研究显示有 CMV 感染史较无 CMV 感染史的患者 NODAT 发病风险增加 1.464 倍^[8], 其机制可能与 CMV 感染后直接或间接产生 IL-1 β 、TNF- α 等促炎细胞因子诱导胰腺 β 细胞损伤, 从而导致胰岛素释放减少有关^[20-21]。Peled 等的研究证明心脏移植术后的低镁血症可导致 NODAT 发生风险显著增加 8 倍以上, 是 NODAT 的独立预测因素, 并指出其中重要原因是移植术后 CNI 药物应用诱导的尿镁排泄^[19], 而镁是参与葡萄糖代谢的重要因子, 镁缺乏会促进胰岛素抵抗导致糖代谢异常^[22-23]。多项临床研究表明冷缺血时间的延长也是 NODAT 的重要危险因素^[10,24], 动物实验研究发现冷缺血时间延长与较强的排斥反应以及更重的移植血管疾病有关^[25], 因此可能会导致术后免疫抑制剂的使用增加, 进而增加 NODAT 的发病风险。

2 冠脉血运重建术后新发糖尿病的危险因素

2.1 人口学因素

与 NODAT 相同, 基线 BMI 也是冠脉血运重建术后新发糖尿病的关键风险因素之一。研究表明, 基线 $BMI \geq 25 \text{ kg/m}^2$ 与血运重建术后新发糖尿病的发病风险增加密切相关^[2]。在 1 年内 BMI 每增加 1 kg/m^2 , 术后新发糖尿病风险增加 1.14 倍^[26]。目前尚未发现性别以及年龄与冠脉血运重建术后新发糖尿病有显著关联^[2,27]。

2.2 糖脂代谢状态

冠脉血运重建术中, 除血糖水平外, 血脂水平与术后新发糖尿病的发生也存在相关性。研究发现基线高随机血糖和高甘油三酯 (triglycerides, TG) 水平均是 PCI 术后新发糖尿病的危险因素^[27], 而基线高密度脂蛋白胆固醇 (HDL-cholesterol, HDL-CH) 水平则与冠脉血运重建术后新发糖尿病风险呈负相关^[26]。

2.3 用药因素

大量循证证据表明他汀类药物可明显降低冠心病患者的冠脉事件风险及重复血运重建率^[28-30], 是冠脉血运重建术后的基础用药之一。然而目前越来越多研究发现, 他汀类药物亦可致胰岛 β 细胞功能受损, 胰岛素敏感性和释放降低^[31], 可显著增加新发糖尿病的风险^[32-33]。有研究对 30 665 名急性冠脉综合征 (acute coronary syndrome, ACS) 行 PCI 术后的患者平均随访 3.14 年发现, 服用他汀类药物使 PCI 术后新发糖尿病风险显著增加 27%^[34]。不同种类的他汀类药物对新发糖尿病的影响不同, 多项研究显示急性心肌梗死 (acute myocardial infarction, AMI) 患者在进行血运重建术后, 与使用阿托伐他汀和瑞舒伐他汀治疗相比, 中等强度匹伐他汀的新发糖尿病风险较小且临床结局相似^[35-36]。不同降脂强度对于新发糖尿病的影响则存在不同的研究结果。一项纳入了 32 752 名患者的 Meta 分析结果表明, 高强度较中等强度他汀治疗的新发糖尿病风险增加 12%^[37]。然而 Ko 等的研究发现高强度和中等强度的他汀类药物治疗对于因 ACS 行 PCI 等血运重建术后患者的新发糖尿病并没有显著影响^[38]。Jeong 等的研究针对匹伐他汀的不同剂量与新发糖尿病风险未见显著差异^[39]。

3 小结与思考

心脏手术作为一种侵入性操作, 可能引起术中胰岛素敏感性的部分损害。因此, 易出现术后短暂血糖升高的现象。当前许多研究也多以心脏术后的应激性高血糖状态作为研究重点^[40-42], 而较少关注术后所形成的长期稳定糖尿病状态。现有证据提示心脏术后患者远期发生糖尿病的风险也较高^[2-3], 其中术后长期用药是重要的危险因素之一。

他汀类药物不仅是冠心病二级预防及冠脉血运重建术后的基石, 也是心脏移植术后血脂异常的首选治疗药物^[43], 具有较好的安全性和可耐受性^[44]。虽然目前认为他汀类药物存在引起新发糖尿病的发生风险, 但大量研究也证实其心血管获益显著超过新发糖尿病的不利影响^[45-46], 亦有研究显示他汀类药物仅增加已具有多个糖尿病危险因素的心脏术后患者的新发糖尿病风险^[47]。值得关注的是, 近年来新型降脂药前蛋白转化酶枯草溶菌素 9 (proprotein convertase subtilisin/kexin

type 9, PCSK9) 抑制剂可安全有效的降低心脏术后糖尿病患者的血脂水平, 具有显著的心血管获益且不增加新发糖尿病风险^[48-49], 未来具有较好的临床应用前景。有研究显示, 在冠脉血运重建术后患者的调脂治疗中, 相较于基线时无糖尿病患者, PCSK9 抑制剂阿利西尤单抗对于同时伴有糖尿病的患者成本获益更高, 但是对于避免新发糖尿病事件和成本效益之间的比较有待进一步阐明^[49]。

心脏术后新发糖尿病是多因素共同作用并相互影响的结果, 其具体机制有待阐明。对术后新发糖尿病的早期发现和积极管理是促进心脏手术患者临床获益的重要内容。如在早期筛查方面, 口服葡萄糖耐量试验 (oral glucose tolerance test, OGTT) 虽较为费时, 但较糖化血红蛋白 (glycated hemoglobin, HbA1c) 和 FPG 的灵敏度高, 有助于早期发现 NODAT 患者。因此建议对 NODAT 高风险患者采用 FPG、HbA1c 联合 OGTT 方式进行筛查, 筛查频率为术后 4 周每周一次, 术后 1 年内每 3 个月一次, 之后每年一次, 并在调整免疫抑制剂和激素等药物治疗时及时筛查^[50]。目前缺乏关于冠脉血运重建术后新发糖尿病的筛查指南, 考虑到冠脉血运重建术和心脏移植术均存在手术应激和术后长期用药的情况, 因此可一定程度参考 NODAT 筛查方式, 如在增加他汀药物剂量后也及时增加血糖筛查等。此外, 为避免术后应激因素等干扰, 建议至少应在心脏术后 6 周待病情稳定及用药相对固定时再确认患者是否处于长期的糖尿病状态^[51]。

心脏术后新发糖尿病危险因素的术前综合评估十分关键, 对高风险患者可尽早对其 BMI、血糖及血脂等可干预因素进行早期筛查和积极控制, 以降低术后糖尿病发生率和预后的改善。但目前对于心脏术后新发糖尿病的研究数量和规模尚不足, 暂未形成公认的心脏术后新发糖尿病风险评分表或标准化的预测模型, 未来应通过开展多中心、大型队列研究以建立规范化、临床应用性强的风险预测模型, 从而实现对心脏术后新发糖尿病的早期管理和综合防治。

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