·综　述　General review·

颈动脉支架内再狭窄研究进展

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【摘要】 颈动脉支架内再狭窄(ISR)是颈动脉支架植入术(CAS)后远期并发症,发生率较高,严重影响患者预后。ISR 发生与多种因素有关。本文在国内外研究基础上,对 CAS 术选择、ISR 发病机制、危险因素、治疗选择及其研究进展作一综述。

【关键词】 颈动脉狭窄;颈动脉支架植入术;支架内再狭窄;血管内治疗
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Research progress in carotid artery in-stent restenosis　*LIANG Guangcai, HUANG Shan, SHI Lei, DENG Gang. Department of Intervention and Vascular Surgery, Affiliated Zhongda Hospital, Medical School, Southeast University, Nanjing, Jiangsu Province 210009, China*

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【**Abstract**】 Carotid artery in-stent restenosis (ISR) is a long-term complication after carotid artery stenting (CAS), which can seriously affect the patient's prognosis, and clinically its incidence is high. The occurrence of ISR is associated to multiple factors. Based on the domestic and foreign researches, this paper aims to make a comprehensive review about ISR, focusing on the selection of CAS, pathogenesis, risk factors, treatment selection and its recent research progress. (J Intervent Radiol, 2023, 32: 396-399)

【**Key words**】 carotid stenosis; carotid artery stenting; in-stent restenosis; endovascular treatment

颈动脉支架植入术(carotid artery stenting,CAS)具有禁忌证少、术后恢复快、效果确切等优点,广泛应用于治疗颈动脉狭窄。该术式并发症之一支架内再狭窄(in-stent restenosis,ISR)发生率较高,且会增加患者复发性脑卒中风险。本文就 CAS 选择及 ISR 发病机制、影响因素、治疗方法等研究进展作一简要综述。

1　颈动脉狭窄流行病学和病因

近期柳叶刀子刊一大型 Meta 分析表明，全球(包括中国)30～79 岁人群中颈动脉内膜-中膜厚度增加(≥1.0 mm)的人群约占 27.6%,颈动脉内膜-中膜厚度增加预示斑块形成,而颈动脉斑块发生率约为 21.1%,颈动脉狭窄约为 1.5%,这一数据在男性中为 1.8%,女性为 1.2%[1]。随着年龄增长,颈动脉斑块和颈动脉狭窄发生率持续增加,男性同期总是高于女性;90%以上颈动脉狭窄是动脉粥样硬化斑块所致;动脉粥样硬化是一慢性炎症过程,慢性炎症刺激会引起血管狭窄,甚至闭塞,导致颅内缺血、梗塞,不稳定性动脉粥样硬化斑块破裂会触发血小板活化和血栓形成,也可引起脑血管缺血和梗死[2]。多项研究表明，缺血性脑卒中 15%～25%与颈动脉粥样硬化斑块所致狭窄有关,通常发生于颈总动脉分叉处,即颈内动脉起始段[3-6]。

2　粥样硬化所致颈动脉狭窄

2.1　狭窄测量和分级

粥样硬化所致颈动脉狭窄测量和分级在不同指南中存有差异,临床广泛接受的是欧洲颈动脉外科试验(ECST)[7]和北美症状性颈动脉内膜切除试验(NASCET)[8]研究中所制定的测量方法和分级标准,其中 NASCET 方法和标准应用较普遍,其测量方法是在患者 DSA 图上测量最大狭窄点和颈内动脉正常部位管腔直径,并通过测得值比值确定狭窄

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占比，定义狭窄率 0%～29%为轻度狭窄、30%～69%为中度狭窄、70%～99%为重度狭窄。

2.2 治疗选择

粥样硬化所致颈动脉狭窄治疗包括最佳治疗(使用适当药物、控制危险因素和调整生活方式)、颈动脉内膜剥脱术(carotid endarterectomy,CEA)及血管内治疗,均旨在降低缺血性脑卒中风险、改善脑缺血症状和预后。根据欧洲血管外科学会(ESVS)2021 年版颈动脉狭窄治疗指南,药物治疗和改变生活方式是颈动脉狭窄治疗基石，对狭窄程度＜60%无症状患者应首先予内科药物治疗并控制危险因素,再基于危险分层确定是否需行 CEA 或血管内治疗;狭窄程度 60%～99%无症状患者脑卒中风险大大增加,推荐行 CEA 术;对狭窄程度 70%～99%有症状患者推荐行 CEA 术;对狭窄程度 50%～69%患者,尤其是＞50%、年龄＜70 岁有症状患者,也可考虑行 CAS 术[9]。然而,颈动脉狭窄 CEA 术应用常受限于患者同时存在多种基础疾病、血管解剖不利(颈动脉迂曲、术区显露困难等)及可能发生相关并发症等。随着近年神经介入技术、硬件设备、支架材料研究发展,SAPPHIRE、CREST、ACT-1 及 ACST-2 等多项大数据临床试验研究均表明,有症状或无症状颈动脉狭窄患者 CAS 术和 CEA 术后脑卒中、心肌梗死,甚至死亡等主要安全性结局风险比较差异均无统计学意义，围手术期 CAS 术脑卒中风险较高,CEA 术心肌梗死风险较高[10-13]。由于手术创伤较小、卧床时间和住院周期较短、患者满意度较高,CAS 术临床应用越来越广泛。

3 CAS 术后 ISR

3.1 发病率

CAS 术后 ISR 使患者面临复发性脑卒中和神经系统疾病风险。研究表明,CAS 术后 ISR(≥50%)患者 6 年累积发生同侧复发性脑卒中风险为 12.0%,而未发生 ISR 患者为 8.1%[14-15]。多项大型研究报道 CAS 术后 ISR 发生率为 2.7%～40.7%,其中 ICSS 研究表明术后 5 年累积复发性脑卒中风险在中度 ISR(≥50%)患者为 40.7%,重度 ISR(≥70%)为 10.6%[14-21]。CAS 术后 6 个月内 ISR 患者发生短暂或永久性同侧眼部或脑部缺血事件则表明有症状[10,15,22-23]。

3.2 发生机制

ISR 发生机制比较复杂，大部分学说支持其由内膜增生(内皮损伤后引起内膜反应性增厚)和动脉重塑(血管管径大小改变)导致,其中新生内膜是其基本变化[24]。进一步研究认为,内膜增生与血管重塑间可能存在相关性,即血管扩张可能是对内膜增生的适应性反应(血管补偿由内膜增厚产生的管腔狭窄)[25]。CAS 术后对血管内皮产生一定损伤并通过炎性介质触发内膜增生,随着时间进展,血小板聚集、炎性细胞浸润、生长因子释放以及平滑肌细胞和细胞外基质积累构成了 ISR 成熟斑块的主要成分[26]。同时,许多研究在分子机制上阐述 ISR 相关因素，如细胞外基质中胶原蛋白积累及调节因子[26]、miRNA-501-5p 分子介导的血管平滑肌细胞表型[27]、干扰素-γ 受体[28]、RNA 某些基因(CYP7A1、CDK4)等表达,均与 ISR 相关[29]。有研究认为,CAS 术后局部血流动力学因素改变等均与 ISR 相关[30]。ISR 早期主要表现为动脉内膜新生，这是一种偏良性 ISR,多在 CAS 术后 2 年内发生,远期主要表现为动脉粥样硬化,是粥样硬化斑块持续进展的缘故[26]。

3.3 危险因素

许多研究报道与 ISR 相关的危险因素,主要包括女性、高龄、糖尿病、血脂异常、吸烟、高血压、肥胖、初始狭窄严重程度、残余狭窄程度、斑块钙化、斑块长度、支架长度和直径、用药情况等[7-8,14,19,21]。

3.4 治疗选择

现今针对 ISR 主要有最佳药物治疗(best medical treatment,BMT)、血管内治疗及外科手术。单纯 BMT 主要包括抗血小板、他汀降脂类等药物治疗。研究表明,BMT 对于大多数 ISR 患者有效，可降低早期复发性脑卒中风险，但对于部分患者效果不佳,可能需要更积极治疗[31]。2018 年 ESVS 指南推荐应用与原发性动脉粥样硬化狭窄症状患者相同标准治疗 CAS 术后无症状 ISR 患者，且 2021 年最新版指南并未对此更新：若药物治疗无效甚至 ISR 进展,可考虑再行 CEA 或 CAS 治疗；若出现同侧颈动脉症状且狭窄程度为 50%～99%,则应在 14 d 内再行 CEA 或 CAS 治疗[32]。有研究纳入 35 项 CAS 术后 ISR 治疗文献共 1 359 例患者，结果显示 66.3%患者再行 CAS(rCAS)治疗,其次为再行经皮腔内血管成形术(PTA)(17.5%)、CEA(14.3%)、颈动脉旁路移植术(1.5%)及外照射放疗(0.4%);再行 PTA、rCAS、CEA 治疗后脑卒中和短暂性脑缺血发作(TIA)发生率相似,分别为 1.1%、1.1%、1.5%,差异无统计学意义,术后死亡率 CEA(2.5%)略高于 rCAS(0.7%),差异无统计学意义；结论认为 rCAS 是 ISR 最常用治疗方法，术后及远期风险低,CEA 为 rCAS 重要替代方案,不推荐 PTA[33]。另一 Meta 分析纳入 11 项研究共

1 057 例 ISR 患者，结果显示 rCAS 术安全有效，较常应用于治疗原发性 CAS 术后严重或症状性 ISR 患者，其近期和中期脑卒中、死亡及手术相关并发症结局相似[34]。单纯 PTA 效果持续短，再狭窄风险较高，这是因为球囊扩张挤压斑块的同时有可能引起血管壁受损，内膜-中膜撕裂造成管腔局限性扩大，血流灌注虽得到恢复，但纤维组织修复内膜-中膜增生同样可能再次引起狭窄。许多研究显示，药物洗脱球囊(DEB)治疗具有较好的安全性和可行性，中远期疗效良好[35-40]，紫杉醇为常用涂层药物。本中心近两年多次应用 DEB 治疗颈动脉狭窄及 ISR，预期疗效较常规 PTA 优越。有研究报道应用切割球囊血管成形术(CB-PTA)治疗 ISR 长期随访患者，结果显示治疗安全有效，远期通畅率较好[39-40]。此外，有研究报道采用药物洗脱支架(DES)植入术治疗 ISR，结果显示通畅性较好，但也出现急性支架内血栓形成，原因可能是 DES 阻止平滑肌细胞增殖，但同时阻止血管内皮细胞增殖，导致内皮细胞无法及时修复覆盖管腔，引起持续性炎性反应[41]。有研究报道采用 DES 植入术治疗 7 例 ISR 患者，17 个月随访中有 5 例未发生再狭窄，2 例发生动脉闭塞[42]。目前 DES 植入术在冠状动脉、外周动脉 ISR 应用较多，但在颈动脉 ISR 应用仍较少，使用药物除了常规紫杉醇和西罗莫司外，还有部分新型药物如三氧化二砷[43-44]、靶向 Sp-1 蛋白[45]、RhoA 抑制剂[46]等，均通过 YAP 信号传导通路增强血管平滑肌细胞作用、抑制 ISR，相关动物实验在持续进行。

4 展望

PTA 和 rCAS 是目前治疗 ISR 最常用方法，DEB 和 DES 远期通畅性和安全性尚待更多样本研究结果加以验证。密网支架、双层支架、生物可降解支架、新型金属合金支架和放射性支架等正在兴起，已在颈动脉狭窄及 ISR 患者中得到进一步研究和应用，其安全性和远期通畅性有待进一步观察[47-50]。

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