

血流导向装置植入术后支架内狭窄的血流动力学机制、评估方法及治疗研究进展

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【摘要】 血流导向装置(FD)植入术已广泛应用于颅内动脉瘤的治疗。支架内狭窄(ISS)是FD植入术后的常见并发症,可导致缺血性事件并影响患者预后。ISS的发生与血流动力学改变密切相关。本文从血流动力学角度出发,围绕FD植入术后ISS的发生机制、评估方法及治疗的研究进展进行综述,以期为临床实践提供参考。

【关键词】 血流导向装置; 支架内狭窄; 血流动力学; 壁面剪切应力; 环壁张力

基金项目: 国家自然科学基金(81974177)

DOI:10.3760/cma.j.cn115354-20241206-00765

Recent advances in mechanisms, evaluations and treatments of in-stent stenosis following flow diverter implantation from hemodynamics perspective

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【Abstract】 Flow diverter (FD) devices have gradually become the mainstream approach for interventional treatment of intracranial aneurysms. In-stent stenosis (ISS) is a common complication after FD implantation, which can lead to ischemic events and affect the prognosis of patients. Current studies have shown that ISS occurrence is closely related to hemodynamic changes. From the perspective of hemodynamics, this article reviews the research progress of mechanisms, evaluation methods and treatments of ISS after FD implantation, in order to provide reference for clinical practice.

【Key words】 Flow diverter; In-stent stenosis; Hemodynamics; Wall shear stress; Circumferential wall tension

Fund program: National Natural Science Foundation of China (81974177)

DOI:10.3760/cma.j.cn115354-20241206-00765

血流导向装置(flow diverter, FD)作为一种安全有效的血管内治疗工具,已广泛应用于颅内动脉瘤的治疗,其通过改变血流动力学模式,减少动脉瘤内血流冲击和压力,促进颅内动脉瘤的闭塞,尤其对大型或巨型、宽颈动脉瘤显示出良好的临床效果^[1-3]。近年来,FD的适应证逐渐扩大,已用于治疗破裂动脉瘤、远端动脉瘤等,进一步推动了其临床应用^[4]。然而,FD植入术后也伴随一些并发症,例如支架内狭窄(in-stent stenosis, ISS)平均发生率为8.8%^[5]。ISS可影响FD的治疗效果,导致脑缺血事件并增加再治疗风险。研究

表明,ISS多发生在FD植入术后6个月内,其血流动力学机制复杂,涉及多因素交互作用^[6]。探讨FD植入术后血流动力学的变化规律,对预防ISS、优化FD设计及临床应用策略、改善颅内动脉瘤患者预后具有重要指导意义。本文从血流动力学角度出发,围绕FD植入术后ISS的发生机制、评估方法及治疗的研究进展进行综述,以期为临床实践提供参考。

一、ISS 的概述

ISS是指FD植入术后,患者血管直径因血流动力学变化

而变窄,导致内膜增生或血栓形成。ISS 的狭窄率计算公式^[7]: 狹窄率(%) = $(1 - \frac{\text{狹窄直径}}{\text{参考血管直径}}) \times 100\%$, 其中参考血管直径为支架植入前的血管直径,狹窄直径为随访时的血管直径。FD 植入术后 ISS 会显著减少血流量,并增加血栓形成和缺血性并发症风险,影响颅内动脉瘤患者的预后^[8-9]。

ISS 狹窄程度的分级标准在不同研究中有所差异。Essbaiheen 等^[10]和 You 等^[11]按狹窄率的不同将 ISS 狹窄程度分为轻度狹窄(<25%)、中度狹窄(25%~50%)、重度狹窄(>50%); Wang 等^[12]和 Chalouhi 等^[13]分为轻度狹窄(<50%)、中度狹窄(50%~75%)、重度狹窄(>75%); Gui 等^[7]分为轻度狹窄(50%~70%)、重度狹窄(>70%)、闭塞(100%)。FD 植入术后 ISS 的平均发生率为 8.8%,范围为 0.2%~44.0%。Ravindran 等^[14]系统综述了 43 项研究,报告 FD 植入术后 ISS 的平均发生率为 8.8%。国内一项研究显示 FD 植入术后 ISS 的发生率为 8.4% (111/1 322)^[15]。Sweid 等^[16]分析了 598 例 FD 植入术后患者,ISS 发生率为 6.3%。Gui 等^[7]长期随访显示,FD 植入术后患者中约 15%发生了 ISS。ISS 发生率的差异可能是因为研究中纳入标准、患者特征(如年龄、动脉瘤位置)、支架设计及随访时间不同所致。

ISS 的病理生理机制是一个复杂的多阶段过程,涉及多种因素的交互作用。FD 植入术后,血管内皮损伤引发血小板聚集和白细胞浸润,诱发局部炎症,释放生长因子和细胞因子,促进平滑肌细胞(smooth muscle cells, SMCs)增殖与迁移,导致内膜增厚和肉芽组织形成,最终形成 ISS^[6,17]。支架材料(如镍钛合金)可能诱发局部炎症,抗血小板治疗不足则加剧 ISS 的发生风险^[18-19]。此外,患者年龄、动脉瘤位置、支架贴壁不良或支架尺寸不匹配时可影响血流动力学,进一步促进 ISS 的形成^[12,20]。

二、FD 植入术后血流动力学的变化

FD 植入术后局部血流动力学发生变化,将血流从颅内动脉瘤囊内转至载瘤动脉,降低了动脉瘤内的血流冲击和压カ,从而促进血栓形成及闭塞^[21]。FD 植入术的治疗效果依赖于多种血流动力学参数的协同变化。

FD 植入术后,动脉瘤颈部的血流速度及壁面剪切应力(wall shear stress, WSS)发生显著改变,主要表现为:(1)瘤颈部血流速度降低;(2)WSS 重新分布。这种血流动力学变化可调控内皮细胞的增殖与修复,促进瘤颈部新生内皮覆盖,最终实现动脉瘤闭塞^[21-23]。FD 植入术导致动脉瘤颈部及其远端的血流动力学发生区域性改变,直接减少了进入动脉瘤囊内的血流量,优化了载瘤动脉的血流分布,提升了治疗的安全性和有效性^[24]。压力梯度也在 FD 植入术后发生重要变化。Kim 等^[24]研究发现,当 FD 直径与载瘤动脉不匹配时,局部压力梯度异常升高,可导致血流紊乱,影响疗效。

FD 的高金属覆盖率(35%~55%)和孔密度(45%~60%)诱导动脉瘤内涡流强度增加。Mutlu 等^[25]研究发现,涡流强度增加能显著促进血流停滞,为血栓形成创造有利条件。能力损耗(energy loss, EL)同样也是反映血流效率的关键指标。Zhang 等^[26]通过 Meta 分析得出结论,FD 植入术后 EL 的

变化以降低为主,其中动脉瘤愈合与 EL 降低显著相关。然而,Peach 等^[27]通过对 3 个分叉动脉瘤的模拟研究发现 FD 设计参数(孔隙率、密度)、放置准确性及远端血流动力学补偿均可能引起 EL 的局部异常升高,增加动脉瘤破裂的风险。

振荡剪切指数(oscillatory shear index, OSI)与相对驻留时间(relative residence time, RRT)的变化也是 FD 植入术后血流动力学变化的重要表现。Boniforti 等^[28]通过计算流体力学(computational fluid dynamics, CFD)方法研究表明,FD 植入后动脉瘤内的 OSI 显著增加,时均壁面剪切应力(time-averaged wall shear stress, TAWSS)降低,促进了血栓形成。FD 植入术后 RRT 的增加主要源于 TAWSS 降低和 OSI 升高的协同作用,可延长血小板与内皮接触时间,促进血栓形成。Liu 等^[29]对 113 个未破裂颅内动脉瘤的分析表明,RRT 升高对动脉瘤壁重塑及炎症反应等病理过程有显著影响。

三、ISS 的发生机制

FD 植入术后血流动力学的变化是 ISS 发的关键驱动因素。这些变化涉及 WSS、环壁张力(circumferential wall tension, CWT)和血流模式的相互作用,共同促进 ISS 的形成。WSS 是流体对血管内壁的切应力,其异常变化直接影响内皮功能。低 WSS(<0.4 Pa)诱导内皮细胞功能障碍,减少一氧化氮合成并上调促炎因子,促进内膜增生^[3,24]。You 等^[30]采用 CFD 模拟分析证实,Pipeline 血流导向装置(Pipeline embolization device, PED)覆盖分支动脉后,低 WSS 区域显著扩大,与 ISS 发生呈正相关。与此同时,高 WSS(>10 Pa)则可能导致斑块不稳定,加剧血管壁损伤^[31]。

FD 植入术后,CWT 的改变进一步加剧了 WSS 异常引发的内皮病理反应。CWT 作为血管壁承受的径向扩张力,受 FD 机械特性和膨胀程度的直接影响。FD 植入后,CWT 异常升高可引发内弹力层损伤和慢性炎症反应,刺激平滑肌细胞增殖和内膜重塑^[32]。Abramyan 等^[33]通过对 2 350 例 FD 植入后颅内动脉瘤患者的回顾性分析发现,CWT 异常与 ISS 风险高度相关($P < 0.01$),尤其是 FD 的尺寸不匹配时更为明显。这表明 FD 的选择和释放技术对预防 ISS 具有重要意义。

血流模式变化作为 WSS 和 CWT 共同作用的下游效应,通过塑造特定的血流微环境,深度参与 ISS 的形成过程。FD 植入术后,局部血流速度降低和涡流形成不仅重塑了动脉瘤内的血流动力学,也改变了支架区域的流体力学特性。低速血流和涡流增强促进血流停滞,增加血栓形成风险^[25]。这与 Monteiro 等^[9]通过光学相干断层扫描观察到的现象一致——PED 狹窄区域常伴有血栓附着,随后被新生内膜覆盖,最终形成 ISS。以下 3 种机制的交互作用构成了 ISS 发展的完整路径:低 WSS 首先诱导内皮损伤和炎症反应,CWT 异常通过机械应力加剧内膜重塑,而血流模式紊乱(低速和涡流)在此基础上促进血栓形成,三者协同作用最终导致 ISS。多项临床研究已证实这一病理生理级联反应是优化 FD 设计和临床应用策略的重要理论基础^[30,34]。

四、ISS 的评估方法

数字减影血管造影(digital subtraction angiography,



DSA)被视为评估ISS的金标准,但无创评估FD植入术后血流动力学的变化,是评价FD治疗效果和判断预后的重要手段。CFD作为高精度血流模拟工具,可定量分析血管内血流速度、WSS和压力分布等关键参数。Stahl等^[35]研究表明,CFD预测ISS的敏感性达85%、特异性达80%,能精确模拟低WSS区域(<0.4 Pa)与内膜增生的相关性,为干预策略制定提供理论依据。然而,CFD分析耗时长(通常需数小时至数天)、成本高且操作复杂,需专业人员和设备支持,这在一定程度上限制了其临床应用。

四维流量磁共振成像(four-dimensional flow cardiovascular magnetic resonance imaging, 4D-Flow MRI)通过非侵入性方式提供三维动态血流评估,可测量血流速度、方向和流量等多维信息。Castle-Kirschbaum等^[36]研究显示,4D-Flow MRI能检测到动脉瘤颈部血流速度降低30%~50%的微小变化,揭示ISS早期血流停滞现象;Meirson等^[37]进一步研究发现ISS患者的WSS平均降低至0.3 Pa,提示内膜增生,处于高风险状态。尽管4D-Flow MRI具有非侵入性和高精度(测量误差<5%)的明显优势,但高昂成本和复杂的操作流程仍限制了其在基层医疗机构的广泛应用。相位对比磁共振成像(phase-contrast magnetic resonance imaging, PC-MRI)作为相对简化的技术,主要用于定量测量血流速度和体积流量。Kamada等^[38]研究发现,ISS患者FD区域血流量平均减少约20%(由50 mL/s降至40 mL/s),且血流量减少程度与狭窄严重程度呈显著正相关关系($r=0.82, P<0.01$)。与4D-Flow MRI相比,PC-MRI成本较低,但仅限于二维平面分析,提供的血流动力学信息相对有限。

经颅多普勒超声(transcranial doppler, TCD)和经颅彩色多普勒超声(transcranial color-coded doppler, TCCD)因其便携性、实时性和相对低廉的成本,在ISS的筛查与随访中具有独特价值。Costa等^[39]研究证实,FD植入术后TCD搏动指数升高与ISS的发生风险高度相关($r=0.78$),敏感性达75%;Tony等^[40]进一步验证了TCCD在围术期评估ISS的准确性(与DSA一致性达80%)。超声技术的优势在于可实时、重复监测脑血流的变化,尤其适合术后随访和急诊筛查,但其检测质量受检查者的经验和患者颅骨穿透性的显著影响。

总之,ISS的血流动力学评估需结合多种技术手段。CFD和4D-Flow MRI提供高精度分析但成本较高,适合研究和术前规划。PC-MRI简便但图像处理相对比较复杂,适合二、三级医院检查。TCD/TCCD则平衡了实用性与准确性,因其便捷性特别适用于围术期筛查。临床实践中应根据实际医疗条件、患者具体情况和诊疗需求,选择合适的评估方法,为ISS的早期识别、风险分层和个体化治疗提供依据。

五、ISS的治疗

ISS的治疗策略主要包括抗血小板治疗、血管内介入治疗、覆膜FD应用及FD优化设计等,通过调控血流动力学以缓解狭窄并改善患者预后。

1. 抗血小板药物:抗血小板药物通过抑制血小板聚集,降低血栓形成风险,间接优化FD区域的血流动力学环境。双联抗血小板治疗(dual antiplatelet therapy, DAPT, 如阿司

匹林+氯吡格雷)是预防和治疗ISS的主要策略。Lauzier等^[41]研究23例PED患者发现,DAPT使89%患者ISS无进展,且无新发同侧缺血事件,提示其通过减少WSS区域的血栓负荷,维持血流通畅。Senol等^[42]进一步表明,单抗治疗(如普拉格雷或替格瑞洛)在涂层FD植入术后可降低缺血并发症率(<5%),改善血流速度和局部微循环。这些证据显示,抗血小板药物不仅抑制内膜增生,还通过优化血流动力学参数(如降低涡流强度和血流停滞)间接发挥保护作用。

2. 血管内治疗:血管内治疗作为ISS的直接干预手段,主要通过球囊成形术和支架植入物理扩张狭窄段,恢复血流畅通并优化血流动力学。Geale等^[43]报告,球囊成形术治疗ISS后血流速度提升约30%(从20 cm/s增至26 cm/s),涡流和血流分离现象显著减少,WSS分布趋于均匀,从而降低血栓风险并促进内皮修复。血管内治疗的短期血流提升改善了组织供血,但术后需密切监测血栓风险,以确保长期疗效。

3. 涂层FD治疗:涂层FD技术则从源头着手,通过优化材料的生物相容性和表面特性,显著降低ISS发生率。Abbas等^[44]研究显示,采用新一代FRED X装置(含抗血栓涂层)治疗颅内动脉瘤后,ISS发生率降至3%(较传统FD降低50%),因涂层减少炎症反应和内膜增生,维持WSS在正常范围(0.4~1.5 Pa)。Velvaluri等^[45]提出,薄膜涂层FD通过减少低WSS区域(<0.4 Pa)和血小板粘附,进一步优化血流模式,涡流强度下降约20%。此外,涂层FD(如聚合物或肝素化涂层)增强生物相容性,降低局部血流紊乱,为长期血流动力学稳定提供支持。

4. FD优化设计:FD的优化设计,特别是人工智能(artificial intelligence, AI)辅助设计已成为ISS防治研究的前沿领域。Tikhvinskii等^[46]利用CFD结合支持向量机算法,基于WSS和压力梯度数据预测ISS风险,结果显示准确率达90%。Yamada等^[47]开发基于深度学习的CFD模型,分析FD植入术后血流模式,预测低WSS区域(<0.4 Pa)与内膜增生的相关性,敏感性提升至92%。未来可整合TCCD动态血流速度和DSA形态学参数,开发基于卷积神经网络的实时风险评估工具。

总之,抗血小板药物通过减少血栓优化血流,血管内治疗直接改善血流速度和WSS分布,涂层FD则从源头降低ISS风险,协同作用于血流动力学,结合基于合理的FD优化设计,能显著提升治疗效果。

六、总结与展望

FD植入术后,血流动力学变化既是动脉瘤闭塞的基础,也驱动ISS的发生。低WSS(<0.4 Pa)促进内膜增生,异常CWT和血流紊乱(如涡流增强)进一步加剧狭窄。

然而,ISS的具体血流动力学机制尚未完全阐明,仍需深入研究。未来研究应聚焦于3个关键方向:(1)AI辅助风险评估:基于深度学习的模型整合血流动力学与形态学参数可提高ISS预测准确率并实现FD参数个体化优化,确保WSS维持在生理范围;(2)新型材料研发:新型抗凝涂层和自适应材料技术有望显著降低ISS发生率,同时优化局部血流状态;(3)分子标志物探索:血管内皮炎症反应相关分子作为低



WSS 诱导的早期标志物可提高 ISS 早期诊断敏感性。这些方向的协同发展将为颅内动脉瘤 FD 治疗提供更安全、高效的解决方案,显著改善患者预后。

利益冲突 所有作者均声明不存在利益冲突

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(收稿日期:2024-12-06)

(本文编辑:王志娟)