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血流重建术与血管性认知障碍的研究进展

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摘　要

颈动脉狭窄或大脑中动脉狭窄会导致颅内血流下降，进而导致认知功能障碍，血流重建术是恢复颅内血流的重要方法。血流重建术可降低卒中发病率，提高颅内灌注压，改善脑代谢，从而改善认知功能，但术后高灌注、微栓塞又是引起认知功能下降的另一危险因素，不可忽视的是年龄，基础疾病导致的认知功能下降。目前血流重建术是否可以改善认知功能，仍存较大争议，无症状性颅内血管重度狭窄是否需要进行血流重建术，临床尚无定论。目前将血流重建术与血管性认知障碍研究进展进行综述。

关键词

血流重建术，血管性认知障碍，综述，颈内动脉狭窄

Advances in the Study of Blood Flow Reconstruction and Vascular Cognitive Impairment

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Abstract

Carotid artery stenosis or middle cerebral artery stenosis will lead to intracranial blood flow de-

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cline, leading to cognitive dysfunction. Blood flow reconstruction is an important method to restore intracranial blood flow. Blood flow reconstruction can reduce the incidence of stroke, improve intracranial perfusion pressure, improve cerebral metabolism, and thus improve cognitive function. However, postoperative high perfusion and microembolism are another risk factor for cognitive decline, which cannot be ignored is the decline in cognitive function caused by age and underlying diseases. At present, there is still a great debate on whether reconstructive surgery can improve cognitive function. Whether reconstructive surgery is necessary for asymptomatic severe intracranial vascular stenosis has not been concluded clinically. The research progress of blood flow reconstruction and vascular cognitive impairment is reviewed.

Keywords

Reconstruction of Blood Flow, Vascular Cognitive Impairment, Review, Carotid Stenosis

1. 前言

随着社会老年人口的增长，越来越多的人会存在认知能力下降，无论是轻度认知障碍还是老年痴呆。认知功能下降会降低生活质量，给照料者和医疗保健系统造成负担。然而，越来越多的研究表明，脑血流受损会影响认知功能，血流重建术可改善认知功能。

2. 血流重建术与血管性认知障碍关系

血管性认知障碍(vascular cognitive impairment VCI)是指各种脑血管疾病和相关危险因素导致的从轻度认知障碍到痴呆的一类综合征，涵盖了血管源性认知损害从轻到重的整个发病过程[1]。其常影响高级大脑功能，特别是执行和记忆功能[2]。尽管 VCI 的定义及诊断标准仍有争议,可以将 VCI 依临床特征分类，分为轻度血管认知障碍，血管性痴呆和混合性痴呆，其危险因素包括年龄、高血压、高脂血症、高尿酸血症，糖尿病，心脏病，中风，颈动脉斑块，吸烟，和低教育水平[3] [4]。血管狭窄是导致血流减少，认知功能下降的常见原因。

对颈动脉狭窄患者研究发现，绝大多数(78%)报告有认知障碍[5]。M. Ishikawa 等人使用认知功能量表和单光子发射计算机断层扫描(Single-Photon Emission Computed Tomography SPECT)研究发现，患有严重狭窄性颅内动脉疾病的患者，认知障碍最有可能与广泛的、非选择性的双侧脑血流量(cerebral blood flow, CBF)减少有关[6]。有严重的颅内动脉狭窄性疾病的患者通常表现为认知障碍，而无局灶性神经功能缺损，在磁共振成像(Magnetic Resonance Imaging, MRI)上也没有发现任何病因性病变[7]。

3. 病理生理

血管狭窄会导致脑血流减少，进而使颅内灌注压下降，引起脑代谢异常，影响认知功能。TABASCO 研究证实炎症介质与淀粉样蛋白沉积在卒中后 VCI 的发生发展中起重要作用[8]。Back 等人的研究发现，脑血管闭塞通过阻碍淋巴回流而导致淀粉样蛋白清除障碍，并随着神经炎症因子生成而逐步发展为 VCI [9]。由于远端白质完整性受到长期影响，认知功能下降平均在 2 年后出现[10]。Moretti 等人发现认知障碍患者的 H-alpha/L-alpha 与正常人相比出现异常激活，提示这些脑区发生了相应改变[11]。

大脑网络结构的广泛破坏是导致认知功能下降的又一重要原因[6]。脑血流量与脑代谢密切相关，其调节是由复杂的血管网络介导的。Ishikawa 等报道认知功能与脑灌注密切相关[12]。颈动脉严重狭窄时，侧支血流通过 Willis 环等大血管和表面的小血管，以及脑内的小血管防止血流受限。当脑灌注压(cerebral perfusion pressure, CPP)降低时，则触发血管扩张以维持 CBF。如果灌注压持续不足，自动调节功能受损，组织的血流量降低。为了避免血流量减少，氧提取分数(oxygen extraction fraction, OEF)增加以维持脑代谢[13]。然而，随着灌注压的持续降低，会引起缺血[14]，并对脑组织造成不可逆的损害[15]。OEF 增加和脑血流储备(cerebro vascular reserve, CVR)受损与认知障碍[16] [17]和痴呆有关[14] [18]。Marshall 等研究表明，在有症状的颈动脉疾病患者中，单侧脑灌注不足、大脑半球血流动力学衰竭、OEF 升高与认知障碍有关。与正电子发射计算机断层扫描(Positron Emission Tomography, PET)没有改变的患者相比，有症状的颈动脉闭塞患者中，经 PET 测量的同侧 OEF 增加(≥1.13)与认知功能障碍有关。这种关系也适用于仅有短暂性脑缺血发作(transient ischemic attack, TIA)的患者[17]。

脑血流减少 40%~50%可导致细胞损伤[19]，最终导致神经退行性病变和认知功能障碍[22]。事实上，慢性脑灌注不足与神经元死亡和反应性星形胶质细胞增生有关[15]。Ruitenberg 等认为 CBF 受损是导致杏仁核和海马结构萎缩的危险因素。在 6.5 年的随访期间，与 CBF 减少的受试者相比，脑血管反应性(CVR)更强的个体拥有更大的杏仁核和海马体积，认知能力下降的可能性较小[20]。Haratz 等人进行了测试 CVR 和认知分数。98 例 CVR 受损患者狭窄同侧血流动力学障碍的整体认知评分和执行功能呈负相关[19]。提高 CVR，发现重复、构造能力、记忆、计算和相似性功能改善[6]。认知障碍组的 CVR 与认知正常组有显著性差异，而两组 CBF 无显著性差异[6]。所以脑血流储备与认知障碍密切相关。

4. 血流重建对认知功能的影响

Antonopoulos 等人对 16 项研究进行了 meta 分析，评估了颈内动脉支架置入术(carotid artery stenosis, CAS)前后认知表现，发现支架置入后的整体认知、注意力/精神运动速度和记忆方面的较术前有所改善[21]。Fearn 等使用超声对 159 例有症状的颈内动脉内膜切除术(carotid endarterectomy, CEA)患者的 CVR 进行测量，在术后 2 个月，CEA 患者的记忆力、注意力和准确性均有改善，其中 CVR 受损患者改善最大[22]。Chen 等人比较了 34 例无症状颈内动脉狭窄(asyptomatic carotid stenosis, ACS)患者，这些患者在治疗前和治疗后 3 个月进行 CT 灌注扫描，测量脑血容量(cerebral blood volume, CBV)、CBF 和认知功能，研究的结果证明了脑血流改善与 CAS 后认知改善有关[23]。Baracchini 等人的研究发现，有症状患者 CEA 术后的认知能力明显改善，无症状患者的认知功能无明显变化[24]。血流再通可改善认知功能支持了低灌注介导的认知障碍可能是可逆的这一观点[25]。

此外，有些研究显示，血流重建并不能改善患者认知功能。Bossema 等人比较了 56 例计划行 CEA 的严重 ACS 患者、46 例健康对照者和 23 例计划行股浅动脉内膜切除术(REA)的患者，与健康对照组相比，CEA 和 REA 患者的基线认知评估显示，他们在注意力、语言和视觉记忆、运动行为规划和精神运动技能以及执行功能方面的表现有所下降。两组患者在 3 个月和 12 个月时再次接受评估。CEA 和 REA 患者在语言记忆、执行功能和计划速度方面都有显著的改善，但在治疗过程中没有显著的差异。由于 REA 不涉及大脑灌注的改变，所以两组患者的认知能力的提高可能由于手术使心理压力得到了缓解[26]。Lunn 等人回顾了 28 项研究，发现 57%的人报告 CEA 后认知能力改善，而其余 43%的人报告认知能力下降或没有改变[27]。Feliziani 等人研究发现无论手术方式如何，颈动脉血流重建，均不会会改善患者认知功能[28]。

综上所述，血流重建能否改善认知功能仍不能确定，目前正在进行的主要针对无症状性颈动脉狭窄血管再通术及认知功能的多中心、随机对照临床试验(CREST-H)有望发现血管狭窄与认知障碍之间的关

系，可惜目前试验仍在进行中[29]。

5. 评估

VCI 的诊断依赖于广泛的临床评估，包括病理、神经心理测试和多模式神经影像测量[30]。当缺乏合适的大脑样本用于病理诊断时，Skrobot 等人建议使用神经心理学和影像学评估来诊断 VCI [31]。然而，目前还没有针对 VCI 患者的专门神经心理学测试。

神经心理学测试在临床中容易实施，MMSE 量表，MoCA 量表，Mattis 痴呆评定量表，长谷川痴呆量表，神经行为认知状态检查，阿尔茨海默病评价量表，剑桥认知功能检查，韦氏成人智力量表等都可用来评估认知功能，MMSE 与 MoCA 量表应用最为广泛。Xu 等对 102 例皮质下缺血性脑血管病认知功能评估示，MoCA 筛查轻度认知功能障碍敏感度和特异度为 76.7%和 81.4%，MMSE 为 58.1%和 71.2%，认为 MoCA 较 MMSE 更敏感[32]。Dong 等研究发现，MoCA 较 MMSE 敏感，易发现视空间/执行功能，延迟回忆和注意力损害的患者[33]。

大脑的结构变化与 VCI 密切相关，可以通过结构磁共振成像(sMRI)检测到 VCI [29]。Raja 等人利用动态增强 MRI 发现 VCI 的新机制为血脑屏障功能障碍[34]。Suri 等人使用 3.0 TMRI 确定了颅内血管狭窄和认知功能障碍与白质高信号和血管改变的相关性[35]。此外，高分辨率 MRI 的应用可以发现脑血管周围间隙的改变[36]。弥散张量成像(Diffusion Tensor Imaging, DTI)，提示白质结构损伤可成为 VCI 的生物标志物[27]。Williams 等使用图像分割技术预测白质微观结构损伤，可作为 VCI 的替代标记[37]。脑血流动力学灌注，如 SPECT 和 PET，可评价脑代谢水平和血灌流，反映脑功能并提供 VCI 证据[38]。虽然已证实轻度认知障碍与脑葡萄糖代谢过低密切相关，但脑代谢与 VCI 的相关性尚不清楚[11]。

功能磁共振成像(functional MRI)为一种基于血氧水平依赖造影增强原理评估神经功能的有效方法，它测量大脑不同区域中与血流动力学变化引起相关的神经元的活动[39]。在网络层面，Lei 等人通过分析背外侧前额叶皮层和后扣带皮层的低频波动幅值，发现默认模式网络和执行控制网络可以影响 VCI 患者的执行功能[40]。氧-15 正电子发射断层扫描(PET O15)测量脑血流、脑代谢水平，发现颈动脉疾病中认知障碍和胼胝体萎缩有关[41]。

脑电图，反映脑部电生理和脑网络功能，是一种利用非线性动态分析和时频分析，表达信息传送准确性的及时处理力[42]。随着认知功能障碍的进展，脑电图异常程度也加重，特别是事件相关电位，提示脑电图可作为评价认知功能障碍严重程度的可靠客观指标[43]。

功能近红外光谱(functional near-infrared spectroscopy, fNIRS)是一种反映认知水平的新型监测方法。它在认知评价中具有从特殊任务中反映自然情况下的神经功能的优势[44]。Beishon 等人利用近红外光谱法评估脑血流动力学和氧代谢，早期预测认知能力下降[45]。

脑磁图(magnetoencephalography, MEG)是另一种检测更深入的脑动力学方法，其传导效应更小，时间分辨率更高[46]。利用脑磁图，Baillet 总结了脑区域间的功能连通性和脑系统中网络通讯模式的出现的机制[47]。

6. 治疗及进展

治疗认知功能障碍的药物，多奈哌齐和加兰他敏，已被普遍用于治疗 VCI [48]。这些药物对血管性认知障碍可能有改善作用，但疗效尚不清楚。常见不良反应有腹泻、肌肉痉挛、乏力、恶心等。

根据 VCI 的发病机制，推测血流重建可增加脑血流量可以改善认知功能[49]。颈动脉支架植入是一种可以提高脑灌注的方法，通过功能磁共振成像，发现在一定程度上可改善全脑认知和记忆，原因在于增加了左额回的和右额上回与后扣带皮层的连接处的脑血流灌注[50]。Lattanzi 等人的试验表明，随着颈

动脉内膜切除术后脑血管血流的恢复，患者认知能力改善[51]。Mami Ishikawa 等人对脑内大血管狭窄患者行颞浅动脉与大脑中动脉吻合术后，认知能力的改善，提示 CVR 与认知功能相关[12]。Noshiro 等人通过神经成像，证实烟雾病搭桥术后可改善脑的网络结构，提高认知功能[52]。颈动脉狭窄血流重建术可改善患者的认知障碍和 CVR 水平[7]。

虽然神经保护和神经康复已成为治疗 VCI 的重要方法，但神经康复暂无全面可靠的方法以提高患者的认知功能。Perng 等人的 meta 分析发现，症状性认知训练是一种改善认知的有效方法[53]。Ahn 等人研究长期的踏车运动可通过替换缺血海马的多个受损结构来恢复记忆功能，并提示在缺血神经元死亡后开始长期运动可以作为一种慢性神经恢复策略是有效的[54]。

经颅磁刺激(transcranial magnetic stimulation, TMS)可增强脑皮层兴奋性和突触可塑性，提示其可能恢复受损神经的可塑性，并进一步了解神经传递途径在 VCI 发病机制中的作用[55]。

7. 血流重建术后影响认知障碍的原因

众多因素会影响认知功能，例如年龄，基础疾病，术后并发症等。Wasser 等人[56]研究了 CEA 和 CAS 在症状和无症状患者中的认知功能，CEA 和 CAS 在小于 68 岁的患者发现认知功能改善；这在老年患者上并不成立。在 CEA 患者中，年龄和糖尿病增加了认知能力下降的风险[57]。Ortega 等人研究发现，年轻患者的认知功能改善优于老年患者[58]。Borroni 等人对 78 例颈动脉严重狭窄患者行 CEA 后行认知评估后发现，40%的患者认知功能无改善，原因可能是本研究纳入了心力衰竭和心律失常的患者，这些均会影响认知功能[59]。

为了确定术后的高灌注是否与认知功能障碍有关，Ogasawara 等人[60]研究发现有围手术期并发症(如高灌注或脑缺血)的患者中存在认知功能障碍。回归分析发现，围手术期高灌注可预测术后认知障碍。脑高灌注可出现在 CEA 或 CAS 后，继发于自身调节反应的改变，最终导致认知能力下降、毛细血管损伤、坏死和脑出血[61]。

手术相关微栓塞是影响术后认知功能的另一重要原因，术后微栓塞会导致脑微出血，会导致认知功能下降[62]。

8. 研究展望

大部分研究证实了血流重建术可改善患者认知功能。这一结论与运动研究发现老年人运动会使 CBF 的增加、改善认知能力[63]的结果一致。我们期待(CREST-H)发现血管狭窄与认知障碍之间的关系，以助筛选出适合血流重建的人群，提高患者生活质量。

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