·综述·

# 慢性颈内动脉闭塞导致认知功能障碍的研究进展

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**摘　要**：慢性颈内动脉闭塞(CICAO)是认知功能障碍的独立危险因素，可通过多种机制影响脑部结构及血流动力学情况(包括淀粉样蛋白沉积、炎症介质形成、脑灌注不足等)，导致非心脑血管事件风险增加。颈动脉系统重度狭窄或闭塞部位不同所致认知功能减退的表现形式可能存在差异，控制高血压等高危因素可降低其发生风险。临床上对于CICAO患者脑血流动力学情况常用的评估手段为CT灌注成像检查(CTP)，其可能通过间接评估侧支循环及其他血流动力学指标来预测患者出现认知功能减退的风险，但准确性仍有争议。目前临床上常用药物可在一定程度上改善患者的认知功能，尚无根治药物，血管内介入治疗可能通过降低脑梗死再发及改善脑灌注而改善认知功能，但对于纳入患者的标准仍需严格评估，其安全性及有效性仍需进一步探索。该文基于该类疾病的研究现状，对其发病机制、影响因素、评估手段及治疗方案进行综述，以期为临床诊疗及后续研究提供参考。

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**关键词**：脑缺血；颈内动脉；慢性闭塞；认知功能障碍

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## Research progress in cognitive impairment caused by chronic internal carotid artery occlusion

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**Abstract**: Chronic internal carotid artery occlusion(CICAO) is an independent risk factor for cognitive dysfunction. CICAO can affect brain structure and cerebral hemodynamics through multiple mechanisms-amyloid protein deposition, formation of inflammatory mediators, cerebral hypoperfusion, etc. and increase the risk of non-cardio-cerebrovascular events. The manifestations of cognitive impairment vary depending on the site of severe stenos is or occlusion of the carotid system. Controlling the high-risk factors such as hypertension can reduce the risk of cognitive impairment. Computed tomography perfusion imaging is usually performed to assess cerebral hemodynamics for patients with CICAO. It may predict the risk of cognitive decline for patients with CICAO through indirect assessment of collateralcirculation and other hemodynamic parameters, but its accuracy remains controversial. At present, cognitive impairment can be alleviated by the commonly used drugs to a limited extent. Interventional therapy is another approach considered to resolve cognitive decline by reducing the recurrence of cerebral infarction and improving cerebral perfusion, but its inclusion criteria require strict evaluation, and its safety and effectiveness need further exploration. Based on current research on cognitive impairment caused by CICAO, this article summarizes its pathogenesis, influencing factors, evaluation methods, and treatment strategies, in order to provide a reference for clinical management and future research.

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**Keywords**: cerebral ischemia; internal carotid; chronic occlusion; cognitive impairment

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慢性颈内动脉闭塞(chronic internal carotid artery occlusion, CICAO)可表现为无症状或短暂性脑缺血发作(transientis chemic attack, TIA)、中风、进行性视力下降等症状反复发作,也可仅表现为认知功能减退[1]。研究显示,认知功能变化情况可独立预测CICAO患者的生活质量[2],认知功能下降可使患者发生创伤、事故、感染等非心脑血管事件的风险增加,导致死亡风险升高,而在有缺血症状的CICAO患者中,痴呆及认知功能障碍的发生率更高[3]。为进一步了解国内外对慢性闭塞所致认知功能障碍的研究现状,本文拟对其研究进展做一综述,以期为该类患者的临床个体化诊疗提供参考。

## 1 发病机制

炎性介质与淀粉样蛋白沉积在卒中后认知功能障碍的发生发展中起重要作用[4]。Back等[5]认为,大血管闭塞可能会干扰类淋巴通路清除淀粉样蛋白,并伴随神经炎症形成从而导致认知功能障碍。侧支循环失代偿后长期脑灌注不足或皮质及皮质下微梗死也是认知功能障碍的重要机制之一[6],可通过各种信号转导通路如氧化应激、中枢胆碱能系统功能障碍、神经炎症、神经元凋亡和突触可塑性功能障碍等引起神经元死亡[7],最终出现认知功能障碍[8],而脑血管闭塞比狭窄患者更容易出现脑灌注不足[9]。Rosenberg等[10]发现,脑灌注不足导致细胞外基质纤维化并激活神经炎症,对深部白质的损害最大,该类型的多发性梗死和弥漫性白质病变常出现在侧脑室周围和皮质下,导致多认知域损害。此外,Sam等[11]研究认为,单侧颈内动脉闭塞(internal carotid arteryocclusion, ICAO)的患者,由对侧向患侧大脑半球的侧支血流支持是以降低对侧半球的储备能力为代价的,因此,这些病理改变不仅可影响同侧半球,也可影响对侧半球。

## 2 影响因素

年龄、不饱和脂肪酸摄入量、长期吸烟、饮酒等均可通过诱发血管痉挛或改变血糖、血压水平间接导致认知功能障碍[12]。Birkenhager等[13]发现血压水平,尤其是收缩压应维持在一定范围,严格控制血压可防止脑血管损伤和维持足够的脑灌注,有助于降低脑血管事件及认知功能障碍的发生风险。Walker等认为[14],与血压正常的人相比,中年至晚年持续高血压以及中年高血压且老年低血压的患者发生痴呆的风险显著增加。

动脉粥样硬化是ICAO最常见的病因。有研究发现,患有严重动脉粥样硬化的中年人未来可能面临认知功能下降的高风险。此外,结构和功能动脉粥样硬化标志物对认知情况有预测作用,同时存在结构和功能标志物的中年人群,随着年龄增长出现认知功能下降的风险更高[15]。

关于颈动脉系统重度狭窄或闭塞部位不同所致认知功能减退差异的研究,国内外尚未达成一致。有研究认为,左侧颅内动脉闭塞较右侧可能更容易导致认知功能损害[16];单侧闭塞患者认知功能障碍程度总体优于双侧闭塞患者[17]。也有研究认为不同的供血动脉系统狭窄或闭塞,可引起相应脑区的低灌注,继而产生相应的认知功能损害。目前,更多基于影像学的研究使我们能较血管评估更细致的看到脑部结构与功能的关系,如Diciotti等[18]通过功能磁共振成像(functional Magenetic Resonance Imaging, fMRI)检查发现,左侧小脑后部和扣带回皮质中部的高区域同质性可表现整体认知功能尤其是执行功能障碍。

## 3 评估手段

邱炜斌等[19]研究发现,认知功能正常组经DSA评估为侧支血流3~4级的比例明显高于认知功能障碍组,两组CTP参数比较也有明显差异,即脑血流量(cerebral blood flow, CBF)、脑血容量(cerebral blood volume, CBV)较认知障碍组明显升高,平均达峰时间(mean transit time, MTT)较认知障碍组明显缩短,提示CICAO患者认知障碍的发生率与颅内侧支循环代偿程度有关,且CTP可作为侧支血流评估的有效替代方式。Wu等[20]通过对单侧大脑中动脉(middle cerebral artery, MCA)狭窄(闭塞)患者进行CTP算法重建研究同样证实了侧支循环评估的有效性。值得注意的是,尽管CBF与血压水平密切相关,但在老年患者中,CBF可能是认知功能评估的独立预测指标[21]。

此外,CTP对其他血流动力学相关指标的评估也可能具有一定参考价值。氧摄取指数(oxygen extraction fraction, OEF)被认为是评估颈动脉闭塞患者是否需手术再通的有力指征[22]。正电子发射断层扫描(positron emission tomography, PET)是测量OEF的金标准[23],但由于许多医院缺乏PET成像设备,在常规临床中未广泛开展。有研究发现,CTP参数中的MTT与OEF具有最佳关联性,可作为OEF测量的替代方法[24]。Chen等[25]同样认为,CTP获得的MTT可能是可用于评估脑血流动力学的方便且有效手段;脑血流储备(cerebrovascular reserve, CVR)被确定为缺血性卒中的预测因子[26],是评价CICAO的重要指标,也可通过CTP间接评估。

但也有研究对于血流动力学与认知功能的关系提出不同意见,Oudeman等[27]对颈内动脉闭塞(internal carotid artery occlusion, ICAO)合并认知功能障碍的相关文献进行系统性回顾后认为两者的关系仍有待进一步研究,这可能与纳入文献较少,且各文献的入选标准及评价手段不一致有关。

## 4 治疗方案

一些用于治疗阿尔茨海默病的药物,可一定程度上改善认知功能,延缓症状进展,在治疗轻度血管源性认知功能障碍的有效性已得到临床认可[28]。由于目前尚无根

治药物，因此针对多种神经损伤机制的药物联合应用，可能较单药治疗获得的疗效更大[29]。根据认知障碍的发生机制，多奈哌齐等乙酰胆碱酯酶抑制剂已被证实可降低认知功能障碍的小鼠模型在发病过程中的β淀粉样蛋白沉积[30]；兴奋性氨基酸受体拮抗剂，如美金刚胺等，可非竞争性阻断N-甲基-D-天冬氨酸受体，从而改善认知功能[31]。此外，非甾体抗炎药、调脂药物的作用机制主要为抑制环氧化酶-1（COX-1）和环氧化酶-2（COX-2），改善内皮功能，增强神经可塑性，但其在改善认知功能中的疗效仍未确定[32]。最近的一项研究表明，n-棕榈酰乙醇胺-恶唑啉（PEA-OXA）也可以减轻因双侧颈动脉阻塞而导致的血管性痴呆大鼠模型的炎症和氧化应激[33]。

目前对于无症状的CICAO伴I期血流动力学障碍患者是否应该进行血运重建术还存在争议，但对于有症状的I期或II期血流动力学障碍患者，建议进行血运重建[34]。

颈动脉内膜剥离术（carotid endarterectomy，CEA）及颅内外搭桥（intracranial and extracranial bypass，EC-IC）手术均因其手术难度大、成功率相对低、并发症较多，已被证实其疗效并未比保守治疗更佳[35]。RECON试验中，近期存在II期血流动力学损伤的ICAO患者被随机分为EC-IC组（13例）及药物治疗组（16例），以评估血运重建对认知预后的影响，该研究发现两年后手术组和药物组之间的认知变化没有明显差异[36]。Amita等[24]的研究显示，EC-IC未能持续改善认知功能或防止其继续减退，患者术后测定OEF值仍未达正常，提示术后脑灌注仍持续不足，原因可能是尽管改善了同侧大脑中动脉供血区血供，但无法为大脑前动脉供血区及周围分水岭区域提供足够的血流供应。

血管内介入治疗（carotid artery stenting，CAS）改善ICAO患者认知功能的可能机制包括降低脑梗死复发率及改善脑灌注[37]。Kao等[38]对19例颈动脉闭塞合并血流低灌注的患者进行研究可见，成功的颈动脉支架植入术可改善慢性重度颈动脉闭塞患者的长期脑糖代谢和神经认知功能。Fan等[39]进行的一项前瞻性对照研究同样认为，对于症状性CICAO患者，成功的血管内介入治疗可以改善患者的神经功能及整体认知功能。我国一个对照研究对纳入患者进行24个月的随访，证实对于存在单侧前循环大动脉慢性闭塞患者，通过严格的筛选并施行介入再通手术治疗，可使其认知功能得到改善[40]。可见，尽管不同的研究在设计、分析及患者选择上均存在差异，但其结果均表明，CAS可以有效改善血流动力学导致的认知功能障碍[41]。颈动脉闭塞的评分量表（CAO）[42]对血管内开通治疗难易程度及风险获益的预测因子进行综合分析，以此评估介入成功率，Hasan等[43]将CICAO分为4型，并认为A型和B型患者可取得较好的手术结局。这些量表及分型均可在临床诊疗中对CAS患者的选择提供参考。

此外，近期有学者认为，由于大多数颈内动脉闭塞患者的脑血流灌注主要依赖同侧颈外动脉（external carotid artery，ECA）维持，因此，对于合并ECA近端或起始部狭窄的CICAO患者，行ECA支架植入术也可有效改善患者的认知功能[44]。

## 5　总结

综上所述，CICAO是认知功能障碍的独立危险因素，其发病隐匿，可通过多种机制影响脑部结构及血流动力学情况，从而导致认知功能障碍甚至痴呆的发生。因此，对该类疾病进行积极评估及早期干预治疗具有重要意义，血管内介入治疗有望成为该类疾病的有效治疗方案，随着医疗技术及医疗条件的进步，我们期待它更美好的发展前景。

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