



电子、语音版

·综述·

## 成人烟雾病治疗的相关研究进展

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**摘要:**烟雾病(moyamoya disease, MMD)是一种慢性进行性脑血管疾病,涉及颈内动脉末端和/或其近端分支狭窄闭塞,导致侧支血管网形成。这些变化引起脑实质慢性缺血,随后发生严重的脑血管意外。成人MMD患者在未经治疗的情况下会逐渐累及认知功能,且病死率是儿童MMD患者的2倍。由于MMD发病因的复杂性和后果的严重性,该病的治疗尤为棘手且迫切。外科血管重建术作为MMD治疗的基石,主要分为直接血管重建术、间接血管重建术和联合血管重建术三类。考虑到间接血管重建术不能降低围手术期脑卒中的发生率,直接血管重建术通常是缺血型MMD患者治疗的首选术式。若为了预防出血型MMD患者再发出血,选择直接血管重建术或联合血管重建术能够更容易建立侧支循环,促进血运重建,达到治疗的目的。当患者术后出现新发的缺血性卒中,则优先考虑间接血管重建术。对于血流动力学不稳定的成人MMD患者,直接血管重建术或联合血管重建术则是首要选择。由于目前无逆转MMD病情进展的特效药,内科治疗仅局限于对症治疗和围手术期的管理。临床上通常使用阿司匹林抗血小板聚集,促红细胞生成素和他汀类药物等促进侧支血管发育和地塞米松促进新生血管的形成等。远隔缺血适应训练改善MMD患者的后遗症的疗效已经得到了业界的肯定。发病机制研究的深入为MMD的诊疗手段提供更多的可能性。甲硫氨酸循环异常参与了MMD的发病,提示甲硫氨酸循环相关风险评分对烟雾病风险具有良好的预测能力。此外,内皮祖细胞移植可能成为临床上治疗MMD的新策略。

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**关键词:**烟雾病;治疗;血管重建术

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## Research advances in the treatment of moyamoya disease in adults

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**Abstract:** Moyamoya disease (MMD) is a chronic progressive cerebrovascular disease involving stenosis or occlusion at the terminal portion of the internal carotid artery and/or its proximal branches, leading to the formation of networks of collateral vessels. These changes cause chronic ischemia of the brain parenchyma and subsequent severe cerebrovascular accidents. Without proper treatment, adult MMD patients may gradually show the involvement of cognitive function, and the mortality rate of adult MMD patients is twice that of pediatric MMD patients. Due to the complex etiology and severe consequences of MMD, the treatment of this disease is particularly difficult and urgent. Surgical revascularization, as the cornerstone of MMD treatment, is classified into the three main categories of direct revascularization, indirect revascularization, and combined revascularization. Considering that indirect revascularization cannot reduce the incidence rate of perioperative stroke, direct revascularization is often selected as the preferred surgical procedure for patients with

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ischemic MMD. In order to prevent recurrent hemorrhage in patients with hemorrhagic MMD, direct revascularization or combined revascularization can achieve the goal of treatment by establishing collateral circulation and promoting revascularization. When patients develop new-onset ischemic stroke after surgery, indirect revascularization should be selected first. For hemodynamically unstable adult MMD patients, direct revascularization or combined revascularization should be the preferred choice. As there are currently no specific drugs to reverse the progression of MMD, medical therapy is limited to symptomatic treatment and perioperative management. In clinical practice, aspirin is often used to inhibit platelet aggregation, erythropoietin and statins are used to promote the development of collateral vessels, and dexamethasone is used to promote neovascularization. The efficacy of remote ischemic conditioning in improving the sequelae of MMD patients has been recognized by the industry, and in-depth research on pathogenesis may provide more possibilities for the diagnosis and treatment of MMD. Abnormal methionine cycle is involved in the pathogenesis of MMD, suggesting that methionine cycle-related risk scores have a good ability in predicting the risk of MMD. In addition, endothelial progenitor cell transplantation may become a new strategy for the treatment of MMD in clinical practice.

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**Keywords:** moyamoya disease; treatment; revascularization

烟雾病(moyamoya disease, MMD)是一种以双侧颈内动脉虹吸部慢性进行性狭窄或闭塞为特征的脑血管病,常累及大脑中动脉和(或)大脑前动脉始段<sup>[1]</sup>。除传统概念外,近2年,有国外学者提出一种关于MMD的新定义,MMD是一种在儿童期发病,且随着病情发展逐渐影响脑血管系统和全身血管系统的一种血管病变<sup>[2]</sup>。

MMD的临床表现呈多样性,常表现为脑梗死、癫痫、头痛、智力下降和脑出血等。各种症状的发生率与患者的年龄相关<sup>[3]</sup>,其有2个发病高峰,分别在10岁左右和30~40岁。MMD主要分为缺血型和出血型。成人MMD患者容易发生颅内出血<sup>[4]</sup>,多表现为意识障碍,可能由脆弱的新增生的侧支血管破裂或脑室内和蛛网膜下腔的壁瘤破裂所致。

由于MMD的发病机制尚不清楚,且临床症状表现不一,所以目前临床上没有针对MMD治疗的特效药。其治疗主要包括外科手术治疗和内科药物治疗。此外,还有一些新的治疗手段也在临床得到了开展。

## 1 外科治疗

MMD的外科治疗是指外科血管重建术,其目的是减少缺血性或出血性卒中的复发率,并改善患者的神经功能。在过去的几十年中,外科血管重建术对有症状MMD的进展控制效果得到了证实和肯定<sup>[5]</sup>。外科血管重建术的手术类型包括以下3种:直接血管重建术、间接血管重建术和联合血管重建术。

### 1.1 直接血管重建术

在直接血管重建术中,最常见的手术方式为颞浅动脉—大脑中动脉吻合术(superficial temporal artery to middle cerebral artery, STA-MCA)。颞浅动脉分为额支和顶支,其中1支或2支可根据患者临床情况作为供体血管,与大脑中动脉远端分支相吻合。有研究表明,MMD

患者内皮祖细胞(endothelial progenitor cell, EPC)计数高于正常人<sup>[6]</sup>,而SAT-MCA吻合术可以减少缺血型MMD患者的EPC数量,降低侧支再生率,减少脑缺血发作。此外,对于出血型MMD患者的治疗,相比于联合血管重建术,SAT-MCA吻合术是更佳的选择<sup>[7]</sup>,其可以减轻破裂血管的血流动力学压力。而直接血管搭桥术有发生脑高灌注综合征的风险,导致不良的预后。因此,术后急性期应常规监测脑血流量以达到满意的血压控制。

直接血管重建术还包括枕动脉或耳后动脉—大脑中动脉吻合术和枕动脉—大脑后动脉吻合术。当颞浅动脉细小时,可以考虑枕动脉或耳后动脉进行代替与大脑中动脉吻合<sup>[8]</sup>。如果大脑后动脉供血区出现缺血性低灌注,枕动脉—大脑后动脉吻合术可有很好的疗效。

随着技术手段的发展,直接血管重建术已经从单供体单受体发展至双供体双受体甚至单供体双受体<sup>[9]</sup>。相比于单供体单受体,双供体双受体可在2个脑区(额叶和颞叶)进行血运重建,其患者受影响的脑区血运更丰富,预后更好<sup>[10]</sup>。

### 1.2 间接血管重建术

间接血管重建术是指将带血管的组织(肌肉、骨膜、帽状腱膜、硬脑膜或颅外组织等)作为血供来源诱导血管生成的手术。与直接搭桥术不同,间接血管重建术无需血管吻合<sup>[11]</sup>,通常用于MMD儿童患者,而非成人患者<sup>[12]</sup>。间接血管重建术是在血管生成之后开始增加脑血流量,通常需要几个月至1年的时间,因此,间接血管重建术消除了术后脑高灌注综合征的风险<sup>[13]</sup>。

其中,脑—硬脑膜—动脉—血管连通术(encephalo-duro-arterio-synangiosis, EDAS)是最常用的间接血管重建方法之一,其具体步骤为:①仔细分离出颞浅动脉;②沿着动脉双侧切开帽状腱膜,形成含有动脉的腱膜条;③切

开平行于动脉的硬脑膜;④将动脉—腱膜条与硬脑膜缝合起来,使动脉与脑表面连接。EDAS有助于MMD患者形成从颅外到颅内循环的侧支血管<sup>[14]</sup>。有研究已经证实了EDAS对儿童MMD患者具有很好的疗效,不仅增强了手术区域的血液流动,还可以改善由MMD引起的认知功能障碍<sup>[15]</sup>。但是,EDAS仍存在一定局限性,单用EDAS不能满足整个皮质血管的供应,许多患者只能恢复手术周围的区域局部脑血流。

因此,诸多学者提出了EDAS联合其他间接血管重建术的手术方式。Kinugasa等<sup>[16]</sup>提出了将EDAS联合脑—肌—血管连通术的脑—硬脑膜—动脉—肌—血管连通术,这种手术方式可以使缺血脑区的皮质最大化获得血液供应。Kim等<sup>[17]</sup>提出,EDAS联合双额叶脑帽状腱膜骨膜连通术的手术方式,与单纯EDAS相比,该手术显著提高了血运重建率。之后,Park等<sup>[18]</sup>提出了改良版EDAS联合双额叶脑帽状腱膜骨膜连通术的手术方式。这种手术方式可以对大脑前动脉和大脑中动脉覆盖的皮质区域提供充足的血液供应。此外,还有其他文献报道了EDAS联合大网膜移植术,患者均获得了良好的临床结果。

1.3 联合血管重建术

联合血管重建术是指将直接血管重建术和间接血管重建术联合应用的手术方式。联合搭桥术不仅可以通过直接搭桥术立即改善脑血管血流动力学,还可以通过间接搭桥术生成新的侧支循环血管。Tanahashi等<sup>[19]</sup>研究者提出,将使用STA的额支与顶支的STA-MCA双旁路手术与血运丰富的帽状腱膜移植术相结合,结果表明,该手术方式最大限度地增加了间接成分的表面积,同时还可以保持静脉引流,降低静脉充血的风险,对增强MMD患者的血运重建有很好的效果。对于某些在术前有大脑前动脉区域症状的患者,可以考虑大脑中动脉区域的联合

搭桥术。该手术可以改善大脑前动脉区域和大脑中动脉区域的血流动力学,并改善患者预后。

联合搭桥术同样存在一定的缺陷。相比直接搭桥术,其需要更大的手术暴露面积。切口越大,术后组织发生坏死和切口发生感染的风险也就越高<sup>[20]</sup>。联合搭桥术容易引发急性期脑卒中并发症,严重者可导致神经功能障碍。

1.4 3种血管重建术优缺点的比较

以上3种外科治疗方式的优越性存在一定争议,尤其是直接血管重建术与间接血管重建术,哪种方式治疗效果更好并未达成一致共识(表1)。

对于缺血型MMD患者,选择性地采用间接血管重建术不能降低围手术期脑卒中的发生风险,而直接血管重建术可以提供良好的血运重建。因此,直接搭桥术是缺血型MMD患者的首选手术方式<sup>[21]</sup>。Kang等<sup>[22]</sup>的临床研究表明,相比于间接血管重建术,直接血管重建术后的大脑半球的原侧支血管更容易消退,侧支循环也更容易建立。因此,对于预防出血型MMD患者再发出血,直接血管重建术也优于间接血管重建术。

少数患者可能因术后侧支血管供血不足而出现新发的缺血性脑卒中,此时应该优先考虑间接搭桥术。Teo等<sup>[23]</sup>研究发现,重复血管重建可以有效地预防未来缺血性卒中的发生,相比直接搭桥术,间接搭桥术有更高的重复血管重建率。

联合血管重建术和单用EDAS均可降低出血型MMD再出血的风险。Zhang等<sup>[24]</sup>的临床研究表明,在预防再出血事件方面,联合血管重建术优于单独的EDAS。此外,对于有症状或血流动力学不稳定的成年MMD患者,直接搭桥术或联合搭桥术应该作为首要选择(表2)。

表1 3种血管重建术优缺点的比较

项目	直接血管重建术	间接血管重建术	联合血管重建术
优点	对于缺血型MMD患者,可降低侧支再生率,减少脑缺血发作; 对于出血型MMD患者,可减轻破裂血管的血流动力学压力。	无需血管吻合,消除了术后发生高灌注综合征的风险; 易生成新的侧支循环血管; 适用于儿童MMD患者。	迅速改善血流动力学; 易生成新的侧支循环血管; 降低静脉充血的风险。
缺点	易发生高灌注综合征,导致不良的预后。	只能恢复手术周围的局部血液供应。	手术暴露面积大,术后切口发生感染的概率高。

表2 对不同类型MMD患者外科血管重建术的选择

类型	直接血管重建术	间接血管重建术	联合血管重建术
缺血型MMD	首选		
缺血型MMD预防再发脑卒中		首选	
出血型MMD	首选		
出血型MMD预防再发脑出血	首选		首选

2 内科治疗

目前尚未发现可以延缓或者逆转病情进展的特效药,因此,内科治疗主要针对对症处理和围手术期的管理。

有研究发现,阿司匹林纳米粒缓释药能有效提高MMD患者的血小板抑制率,达到更理想的抗血小板聚集作用,有利于改善预后<sup>[25]</sup>。目前尚无神经内科的西地那





略,即基于EPC的细胞治疗。许多动物实验的研究结果对EPC移植的有效性和安全性提供了有力的支持<sup>[38]</sup>。Fang等<sup>[39]</sup>的临床研究发现,自体EPC移植提高了急性脑梗死患者的长期安全性。这些研究都表明基于EPC的细胞治疗策略的可行性。Bayraktutan等<sup>[40]</sup>研究发现,EPC的体外扩增可以促进大量功能性内皮细胞的生长,为该治疗方法成为一种临床治疗产品提供了实验依据。但在其进入临床应用前,仍然需要解决许多问题,如EPC来源(异体或自体)、给药途径、最佳给药剂量等等。

目前,MMD的病因与发病机制未明,患者症状复杂多样,因此临床上极易发生漏诊或误诊。手术治疗是MMD目前有效的治疗手段,但是由于MMD的临床表现没有一致性,不同症状的MMD在不同部位的脑血管病变有不同的首选治疗方案,因此对患者进行个体化治疗显得更为重要。疾病诊断和最佳治疗的根本在于找到确切的发病机制,MMD的发病是由遗传因素和环境因素共同决定的,然而更详尽的机制仍需进一步的研究和探索。相信随着对MMD发病机制的深入研究,MMD的治疗一定可以更加完善。

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