·专题综述·

帕金森病相关呼吸功能障碍研究进展

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【摘要】 帕金森病是临床常见的神经系统变性疾病，可累及呼吸系统，其相关呼吸系统并发症是主要死因，但发病机制及其与帕金森病运动症状和非运动症状严重程度、药物治疗及疾病表型等关系尚未完全阐明。本文综述解剖生理学基础、疾病自身和治疗相关呼吸功能障碍等研究进展，以加深对帕金森病相关呼吸功能障碍的认识，为疾病治疗提供新的思路。

【关键词】 帕金森病； 呼吸障碍； 左旋多巴； 深部脑刺激法； 综述

Progression of respiratory disorders associated with Parkinson´s disease

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【**Abstract**】 Parkinson's disease (PD), a common degenerative disease of the central nervous system, can affect the respiratory system. Pulmonary complications remain its leading cause of death, but the pathogenesis and its relationship to the severity of motor symptoms and non-motor symptoms, medication, and disease phenotype in PD have not been fully elucidated. This article reviews the advances in research on the anatomical and physiological basis, the disease itself and treatment-related respiratory disturbances to deepen the understanding of respiratory dysfunction associated with PD and to provide new insights for treatment.

【**Key words**】 Parkinson disease; Respiration disorders; Levodopa; Deep brain stimulation; Review

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帕金森病是临床常见的黑质多巴胺能神经元丢失导致的神经系统变性疾病，以运动迟缓、肌强直、静止性震颤等运动症状为特征性表现，并伴有便秘、嗅觉减退、抑郁、睡眠障碍等非运动症状，除上述临床表现外，与之相关的呼吸系统症状也是患者倍受困扰的并发症之一。早在1817年，James Parkinson首次描述帕金森病时即提到呼吸系统症状[1]，此后越来越多的文献报道帕金森病患者存在气短、喘鸣、呼吸困难等症状，且其相关呼吸系统并发症业已成为常见病死原因[2-3]。帕金森病患者呼吸系统症状发生率为24.0%～39.2%[4-5]，由于运动症状使患者活动量减少，故呼吸系统症状不易显现，发生率可能被低估。帕金森病早期或症状前均可出现呼吸系统症状，但发生机制及其与运动症状、非运动症状、药物应用和疾病表型等的关系尚不完全清楚；一旦发病即意味着反复住院检查以寻找肺部感染、心力衰竭、肺栓塞或焦虑的证据，给患者和临床医师带来诸多困扰和苦恼。本文拟从解剖生理学基础、疾病自身及治疗相关呼吸功能障碍等方面对帕金森病相关呼吸功能障碍分类及其可能的发生机制进行概述，以期为疾病治疗提供新的思路。

一、呼吸控制的解剖生理学基础

呼吸困难是通气不足、呼吸费力的主观感受，通常与呼吸系统和心血管系统疾病相关。呼吸系统由周围（肺实质、上呼吸道、胸壁、呼吸肌和血管

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系统)和中枢组织结构(脑干呼吸中枢及颈动脉体和主动脉弓化学感受器)组成,任何影响上述结构的病变均可导致呼吸功能障碍。有效通气取决于充分开放的呼吸道、完善的呼吸肌功能和化学感受器对呼吸的正常驱动,因此明确呼吸控制的解剖生理学基础是阐明帕金森病相关呼吸功能障碍发生机制的前提。

帕金森病的病理生理学改变主要为α-突触核蛋白(α-Syn)沉积,中脑黑质致密部多巴胺能神经元凋亡,导致运动控制相关神经回路损伤,随着疾病进展,病变逐渐累及其他部位,包括控制呼吸和睡眠的脑干神经核团[6],最终皮质受累。正常的呼吸节律由脑干呼吸中枢模式发生器(rCPG)产生,通过协调呼吸肌的收缩实现规律的呼吸运动,脑干呼吸中枢主要由延髓以及脑桥背侧和腹侧通气控制中枢组成[7]。根据帕金森病Braak分期以及大量临床研究显示,在疾病发生发展过程中以延髓背侧组织最先受累,其中包括呼吸控制相关蓝斑核[6,8-9],因此在疾病早期即可出现呼吸系统症状。此外,在多巴胺能神经元发生病理改变的同时,星形胶质细胞亦受累,后者作为呼吸中枢的组成部分,可出现相应的病理生理学改变并诱发临床症状[10]。

直立性低血压(OH)在帕金森病患者中较为常见,部分患者出现直立位呼吸困难、平卧位缓解,是由于体位变化后肺尖通气/血流灌注(即每分钟肺泡通气量/每分钟肺血流量比值)失衡所致。存在直立性低血压相关呼吸困难的帕金森病患者自平卧位转换为直立位时血压下降较无呼吸困难患者更为迅速[11-12],且呼吸困难以晨起和饱餐后显著,可能与夜间卧位血压高、夜尿增多所致循环血容量减少、饱餐尤其是高碳水膳食引起的内脏血管扩张和餐后低血压等改变有关[11,13]。

二、疾病自身相关呼吸功能障碍

1.呼吸中枢控制障碍 如上所述,根据帕金森病Braak分期,α-Syn沉积首先发生于脑干,因此帕金森病早期呼吸中枢损伤即可导致呼吸控制障碍和睡眠相关呼吸功能障碍[7,14],同时还有其他机制参与其呼吸中枢控制障碍。fMRI研究显示,大脑皮质、边缘区和副边缘区(皮质-边缘)、小脑均参与呼吸的控制和感知[15];与肺功能正常的帕金森病患者相比,肺功能异常患者左侧海马旁回、右侧梭状回、右侧小脑脚、左侧中央后回等多个脑区灰质体积减小,提示中枢自主神经网络的参与以及灰质的丢失均参与帕金森病的呼吸中枢控制障碍[16]。呼吸控制中枢星形胶质细胞丢失引起的ATP缺乏也可导致呼吸系统症状[10]。通过检测对高碳酸血症和缺氧的通气反应可以评估是否存在脑干呼吸中枢控制障碍,既往研究结论不尽一致,但是均提示帕金森病患者存在呼吸困难的感觉(POD)受损,机体对缺氧和(或)高碳酸血症的感受阈值升高、调控能力减弱。动物实验显示,帕金森病模型小鼠对高碳酸血症的反应减弱,而对低氧的反应正常[14,17-19];临床研究则显示,帕金森病患者对低氧的反应减弱,而对高碳酸血症的反应正常[20-21]。蓝斑核儿茶酚胺能神经元[17],以及蓝斑核和斜方体后核Phox2b神经元[10,17,19]可能均参与二氧化碳浓度升高时的中枢化学反应过程,上述神经元在帕金森病早期即可受累,从而导致对高碳酸血症的调节能力障碍,这可能是脑干呼吸中枢控制障碍的潜在病理生理学机制,但目前相关病理学研究鲜有报道。

2.阻塞性通气功能障碍 帕金森病相关阻塞性通气功能障碍主要表现为上呼吸道阻塞。1984年,Vincken等[22]首次描述上呼吸道阻塞的两种类型,第一种为呼吸震颤,即流量-容积环有规律的振动,频率类似肢体震颤(4~8 Hz),累及声门及声门上结构,但与膈肌振动无明显关联性;第二种为声门及声门上结构不规则、不稳定运动,导致流量-容积环突然和不规则的气流变化,有时可以导致气流中断。帕金森病患者上呼吸道阻塞发生率为6.7%~67.0%[23-25],其发生机制尚不十分清楚,可能与以下因素有关:(1)黑质纹状体多巴胺能神经元丢失导致震颤和运动迟缓等运动症状,随着疾病进展,可在上呼吸道肌肉组织中观察到类似表现[26],咽喉部肌肉的正常功能是维持上呼吸道通畅的解剖生理学基础,咽喉部肌肉功能障碍可以导致上呼吸道阻塞[22,27]。(2)α-Syn病理性沉积不仅局限于脑组织,亦可累及迷走神经及其咽支等支配运动的周围神经,导致声带和咽喉部肌肉功能障碍,出现声带麻痹、喉痉挛和喉部肌张力障碍等[28]。(3)自主神经功能紊乱可以导致上呼吸道运动不协调、张力增高或收缩无力等[29]。(4)被动活动受阻和颈椎关节变形等慢性姿势异常[30]。

3.限制性通气功能障碍 不伴气短、呼吸困难等呼吸系统症状的帕金森病患者也可能存在限制性通气功能障碍,其发生率为28%~94%[25,30-32]。Florêncio等[33]发现,帕金森病患者“开”期和“关”期

均存在限制性通气功能障碍，用力肺活量（FVC）和第1秒用力呼气容积（FEV_1）绝对值显著低于健康对照者，肺胸腔室体积降低，并有55.5%的帕金森病患者存在胸腹矛盾呼吸；此外，“关”期限制性通气功能障碍更严重，表明左旋多巴对帕金森病患者肺功能的改善有益[25,31]。帕金森病患者发生限制性通气功能障碍的机制尚不明确，可能是多种因素共同作用的结果：（1）胸壁和呼吸肌僵硬，肺和胸廓顺应性降低[32]。（2）肋间肌、斜角肌或膈肌震颤导致胸壁、呼吸肌非同步收缩以及胸腹矛盾呼吸[33]。（3）帕金森病相关进行性呼吸肌无力[25,34-35]，快速、重复收缩和震颤可导致呼吸肌疲劳。（4）胸壁僵硬导致的慢性姿势异常尤其是脊柱后凸畸形可限制肺部扩张，进而导致呼吸困难，使肺容积减少[36]。（5）麦角类衍生物导致的胸膜炎、肺纤维化等胸膜和肺相关不良反应[37]。对于早期帕金森病患者，呼气肌无力是唯一的呼吸系统异常表现，并无阻塞性或限制性通气功能障碍[38-39]；而中晚期帕金森病患者，无论“开”期或“关”期均存在包括限制性通气功能障碍在内的肺功能参数明显异常，提示肺功能障碍与疾病严重程度相关[25,35]。2019年，一项来自巴西的帕金森病病例对照研究显示，呼吸肌肌力和肺功能参数异常[包括FVC、FEV_1、呼气峰值流量（PEF）、最大呼气中段流量（FEF 25%～75%）、最大呼气压（MEP）等]与帕金森病相关，并在一定程度上呈负相关，运动迟缓、僵硬等症状越严重，肺功能参数越差[35]，与Baille等[4]的结果相一致。2015年de Campos等[40]研究发现，早期帕金森病模型小鼠仅表现出轻微的限制性通气功能障碍，而膈肌活动度无明显异常；随后他们又在晚期帕金森病模型小鼠中发现其膈肌活动度明显减弱，尤其是阻塞性通气功能障碍明显[41]，限制性通气功能障碍转换为阻塞性通气功能障碍可能反映病变范围的扩大过程，进一步提示肺功能异常改变可能与帕金森病病情进展相关。

4.心因性因素　呼吸困难是一种呼吸不适的主观体验，与健康对照者相比，存在焦虑症状和抑郁症状的帕金森病患者更易出现呼吸困难和肺功能障碍[42-43]。多项研究表明，帕金森病患者的呼吸系统症状主要见于晚期和“关”期，经拟多巴胺类药物治疗后其“开”期肺功能改善、“关”期恶化，出现呼吸困难、气短等症状[32,44]，并与焦虑、抑郁等其他非运动症状伴随出现[4-5,45]。上述研究提示呼吸系统症状可能为焦虑的躯体表现，也可能为帕金森病剂末非运动症状的一部分，属于药物导致的运动并发症，二者的区分尚待进一步探究。

三、疾病治疗相关呼吸功能障碍

1.左旋多巴对肺功能的影响　（1）对肺功能的改善作用：Tandon等[46]对19例肺功能异常的帕金森病患者进行左旋多巴治疗前后的肺功能进行评估，14例基线期存在限制性通气功能障碍的患者治疗后肺功能改善，其中6例恢复正常，5例肺功能无明显改善。一项纳入4项临床试验计73例帕金森病患者的Meta分析结果提示，左旋多巴可以改善患者FVC和PEF，但对FEV_1和FEV_1/FVC比值无明显影响[47]。上述研究结果证实左旋多巴对肺功能具有改善作用，尤其是限制性通气功能障碍，可能与左旋多巴可以协调呼吸肌运动、改善呼吸肌无力的作用有关[39]。多项对比分析左旋多巴对“开”期与“关”期肺功能影响差异的研究显示，帕金森病患者“关”期FVC、FEV_1等肺功能指标下降更明显、呼吸困难更严重，间接证实左旋多巴对肺功能的改善作用[25,31,33,44]。Weiner等[48]发现，左旋多巴治疗后患者呼吸困难减轻，但并不能用呼吸肌肌力或肺功能改善来解释，推测与左旋多巴中枢效应或纠正胸腹矛盾运动有关。（2）对肺功能的负面影响：Lim等[49]对10例帕金森病患者左旋多巴治疗期间及停药前后的肺功能进行评估，结果显示9例患者左旋多巴治疗后出现肺功能异常，但治疗前后各项指标差异无统计学意义；停用左旋多巴后FVC、FEV_1改善，而FEV_1/FVC比值、吸气峰值流量（PIF）或PEF无明显改善。2018年，韩国学者报告1例反复呼吸急促发作的帕金森病合并慢性阻塞性肺病（COPD）患者，左旋多巴激发试验显示其急性呼吸系统症状与左旋多巴相关[50]，可能与左旋多巴诱导的膈肌运动障碍有关[51]，提示左旋多巴可能导致或加重帕金森病患者的呼吸功能障碍。此外，呼吸功能障碍还可以作为左旋多巴治疗的运动并发症，其症状与左旋多巴效应峰值的出现时间相一致，推测与呼吸中枢节律紊乱相关[52]。围手术期或其他原因导致的突然停药或药物急剧减量时可出现急性上呼吸道阻塞，表现为喘鸣、气短、严重呼吸困难，主要是由于喉痉挛、双侧声带麻痹、喉部肌张力障碍所致[53]。既往有多例帕金森病患者全身麻醉术后拔管时出现急性上呼吸道阻塞的报道[53-56]，再次气管插管并予左旋多巴后方可成功拔管[54]，可能与突然停药或药物急剧减量导致的血药浓度急性降低有关，故术后应

尽早恢复药物应用，避免血药浓度剧烈变化，这对早期拔管、撤离呼吸机、减少上呼吸道阻塞发生率具有重要意义。(3)新型左旋多巴制剂：吸入式左旋多巴制剂CVT-301是一种吸入式粉末，采用特制的吸入式给药装置经肺部更好、更迅速地吸收入血，从而缓解帕金森病“关”期症状[57-59]。多项研究评估CVT-301治疗帕金森病的有效性和安全性，包括对肺功能的影响。在LeWitt等[60]进行的为期12周的随机双盲安慰剂对照Ⅲ期试验中，CVT-301组患者FEV_1、FVC和FEV_1/FVC比值等肺功能参数无明显变化，但与安慰剂组相比，治疗后少数患者出现咳嗽(约15%)、咽喉部刺激等不良反应，以及CVT-301(60 mg)相关喘息(1例)和CVT-301(84 mg)相关支气管痉挛(1例)。Grosset等[61]开展的为期12个月的随机非盲法对照试验中，与口服抗帕金森病药物组相比，CVT-301(84 mg)组患者肺功能指标轻微下降，但差异无统计学意义。Farbman等[62]发现，与基线期相比，CVT-301(60和80 mg)治疗后FEV_1、FVC、FEV_1/FVC比值和肺一氧化碳弥散量(DLCO)分别减少0.092 L、0.097 L、0.4%和0.922 ml/(min·mm Hg)，与Grosset等[61]研究中口服抗帕金森病药物组的肺功能指标下降程度相似，提示肺功能下降可能与帕金森病病情进展有关，而与CVT-301无关。上述研究证实吸入式左旋多巴制剂对帕金森病患者的肺功能无明显影响，但不推荐用于合并哮喘、慢性阻塞性肺病或其他慢性肺病的帕金森病患者。因此，对于帕金森病患者即使不存在呼吸困难，左旋多巴治疗前也应行肺功能检测，评估呼吸功能；存在限制性通气功能障碍的患者早期应用左旋多巴制剂对肺功能有一定改善作用，而抗帕金森病药物也可能导致呼吸功能障碍。当患者出现明显的呼吸系统症状时，应详细采集病史，注意症状出现时间、诱因、发作特点、伴随症状(尤其是焦虑、抑郁等)和药物起效时间，必要时可行左旋多巴激发试验以明确呼吸系统症状与药物的相关性。

2.脑深部电刺激术对肺功能的影响　脑深部电刺激术(DBS)是帕金森病晚期治疗的主要方法，尤其是双侧丘脑底核(STN)脑深部电刺激术对帕金森病非运动症状有效[63-69]，但对肺功能的影响尚不明确。2020年，Meoni等[70]首次对STN-DBS对帕金森病患者肺功能的影响进行客观评估，与健康对照者相比，帕金森病患者STN-DBS术后肺功能指标、医学研究委员会呼吸困难量表(MRCDS)和Borg评分均无明显变化。Kawaguchi等[71]对帕金森病患者STN-DBS手术前后非运动症状的频率和严重程度的变化进行评估，发现术后呼吸困难加重，但该研究仅采用问卷调查主观呼吸不适症状，未行肺功能检测。既往认为，帕金森病患者脑深部电刺激术后呼吸困难可能与以下因素相关：(1)呼吸困难的感觉受损[21]，拟多巴胺类药物可改善呼吸困难的感觉，脑深部电刺激术后药物剂量减少，机体对低氧、高碳酸血症的反应减弱，对呼吸功能的调控异常，这是一种术后药量减少导致的剂末非运动症状波动现象。(2)刺激丘脑底核可直接导致会厌固定等咽喉部肌张力障碍[72]。(3)刺激扩散至丘脑底核周围包括皮质核束等其他脑区，可引起喘息、呼吸困难等症状[73]。迄今仅1例个案报道STN-DBS可以改善帕金森病患者呼吸功能，该患者伴左旋多巴剂峰呼吸急促和喘憋，表明呼吸功能障碍作为剂峰异动症的一部分在双侧STN-DBS术后症状完全缓解，可能与其抑制呼吸肌运动障碍有关[74]。亦有个案报道伴左旋多巴剂峰呼吸短浅和胸闷的帕金森病患者存在阻塞性肺功能障碍，单侧苍白球内侧部(GPi)脑深部电刺激术后呼吸系统症状减轻，肺功能改善，但机制尚不十分清楚[75]。近年有研究显示，脚桥核(PPN)与呼吸功能的调控有关[76-79]。目前仅有1项临床研究对PPN-DBS对帕金森病患者呼吸功能的影响进行评估，其结果提示术后最大呼气流速(PEFR)和FEV_1/PEFR比值升高，而FEV_1变化不明显，表明PPN-DBS有助于改善上呼吸道通气功能[80]。目前，关于不同刺激靶点对帕金森病患者肺功能影响的研究较少，且作用机制尚不明确。鉴于目前脑深部电刺激术治疗帕金森病的现状，建议严格筛选手术适应证，术后尽早恢复口服药物的应用，以避免急性呼吸系统并发症的发生[81]；此外，手术前后均应对肺功能进行评估并长期随访，进一步明确脑深部电刺激术对帕金森病患者肺功能的影响，探究其改善帕金森病呼吸功能障碍的潜在靶点和病理生理学机制，以为不同呼吸系统症状的帕金森病患者制定更适宜的手术方案。

四、帕金森病与阻塞性睡眠呼吸暂停综合征共病

近年来，阻塞性睡眠呼吸暂停综合征(OSAS)与帕金森病的关系受到广泛关注，流行病学调查表明有27.6%～70.1%的帕金森病患者可出现阻塞性睡眠呼吸暂停综合征[82-85]。近年研究主要集中在阻塞

性睡眠呼吸暂停综合征对帕金森病临床症状的影响，以及持续气道正压通气（CPAP）在减轻症状和延缓疾病进展中的作用。

一项探究阻塞性睡眠呼吸暂停综合征与帕金森病关系的Meta分析显示，阻塞性睡眠呼吸暂停综合征患者帕金森病发病率是无阻塞性睡眠呼吸暂停综合征患者的1.59倍（95%CI：1.360～1.850，$P<0.001$），尤以老年男性显著[86]。罹患阻塞性睡眠呼吸暂停综合征的患者血浆α-Syn水平升高，提示其可能是帕金森病的危险因素[87]。研究显示，合并阻塞性睡眠呼吸暂停综合征的患者白天过度嗜睡（EDS）、焦虑、抑郁、认知功能障碍等运动和非运动症状相比于单纯帕金森病患者更加严重[83,88-91]；并可出现全面的认知功能障碍，如注意力、延迟回忆、视空间能力和执行功能等认知域损害，且与阻塞性睡眠呼吸暂停综合征严重程度呈负相关[89,91-92]。此外，快速眼动睡眠期行为障碍（RBD）也是帕金森病患者的常见睡眠障碍，合并快速眼动睡眠期行为障碍的帕金森病患者阻塞性睡眠呼吸暂停综合征发病率较低，可能是由于睡眠期肌张力增高，阻碍上呼吸道闭合而发挥保护作用，但同时合并阻塞性睡眠呼吸暂停综合征和快速眼动睡眠期行为障碍的帕金森病患者认知功能障碍更为严重[89]。然而，Shen等[82]发现，阻塞性睡眠呼吸暂停综合征可以加重帕金森病患者的白天过度嗜睡，而与认知功能障碍等其他非运动症状无关联，这是首次以中国帕金森病患者为研究对象探究帕金森病与阻塞性睡眠呼吸暂停综合征共病特征及相关影响因素的研究。上述各项研究所得结论存在差异，可能与所纳入对象的疾病表型、病程、治疗药物等不同有关。因此，阻塞性睡眠呼吸暂停综合征是否为帕金森病的危险因素尚待进一步研究。

Meng等[83]认为，与无阻塞性睡眠呼吸暂停综合征以及合并睡眠呼吸暂停综合征但未予治疗的患者相比，合并阻塞性睡眠呼吸暂停综合征的帕金森病患者持续气道正压通气治疗12个月后统一帕金森病评价量表（UPDRS）评分下降，运动功能维持稳定。Kaminska等[90]为期12个月的随访研究显示，合并阻塞性睡眠呼吸暂停综合征的帕金森病患者经持续气道正压通气治疗后，其睡眠质量、认知功能和焦虑等非运动症状改善。但也有研究显示，持续气道正压通气治疗3周后，治疗组简易智能状态检查量表（MMSE）、蒙特利尔认知评价量表（MoCA）总评分及多项分评分均无显著改善[91]，推测与随访时间较短有关，提示需要更长的治疗时间才能显示出持续气道正压通气的疗效。因此，持续气道正压通气是否可以预防或延缓帕金森病特别是帕金森病痴呆的发生，是否可以作为帕金森病的神经保护治疗方法，尚待进一步研究。与此同时，鉴于运动症状、认知功能障碍和经济水平，长期持续气道正压通气的耐受性和依从性受到限制，其临床可行性有待商榷[93-94]。晚近研究发现一种下颌前移装置可以在改善夜间缺氧的同时，使患者的耐受性和满意度提高，可作为无法耐受持续气道正压通气的患者的替代选择[95]。

综上所述，尽管呼吸功能障碍与帕金森病的病理生理学、临床症状以及药物和脑深部电刺激术的关系尚未完全阐明，但呼吸系统症状对生活质量的影响十分显著，早期识别和预防呼吸功能障碍，及时治疗，可以避免不必要的临床检查和药物应用，同时对预防并发症、改善预后具有重要临床意义。药物治疗尤其是左旋多巴制剂以及脑深部电刺激术对帕金森病呼吸功能的影响结论不一，未来尚待进一步阐明其潜在的病理生理学机制，以更好地制定治疗方案。

利益冲突 无

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下期内容预告 本刊2022年第5期报道专题为血管搭桥术，重点内容包括：脑血管搭桥术50年；椎动脉V3段血管搭桥术研究进展；颞浅动脉-大脑中动脉搭桥术联合颞顶筋膜瓣贴敷术治疗烟雾病疗效分析；烟雾病大脑中动脉供血区血流方向以及顺血流与逆血流搭桥术疗效对比分析；烟雾病患者脑血管重建术后脑过度灌注综合征特点及危险因素分析；成人烟雾病血运重建技术后短期症状改善与神经功能恢复的单中心研究；缺血性烟雾病相对血糖水平与脑血管重建术后并发症相关分析；颌内动脉-桡动脉-脑动脉搭桥术治疗脑血管病回顾研究；基于球囊闭塞试验的脑侧支代偿能力评估及其临床意义；双极电凝分离血管：脑血管重建术中制备供体动脉的新技术