·专题综述·

脑侧支循环评估在急性缺血性卒中机械取栓中的应用进展

王健 夏爽 祁子禹 冯学泉

【摘要】 脑侧支循环对急性缺血性卒中患者缺血半暗带区存活时间至关重要，侧支循环状态与病情进展、血管内治疗后血管再通率、临床预后均密切相关，有必要了解脑侧支循环类型、特点、影像学评价方法及其在急性缺血性卒中机械取栓中的应用进展。

【关键词】 侧支循环； 卒中； 脑缺血； 血栓切除术； 综述

Advances on the application research of cerebral collateral circulation assessment for acute ischemic stroke mechanical thrombectomy

WANG Jian[1], XIA Shuang[1], QI Zi-yu[2], FENG Xue-quan[3]
[1]*Department of Radiology,* [3]*Department of Neurosurgery, Tianjin First Center Hospital, Tianjin 300192, China*
[2]*Grade 2018, Graduate School, Medical College, Nankai University, Tianjin 300071, China*
Corresponding author: FENG Xue-quan (Email: fengxuequan@126.com)

【**Abstract**】 The key to determine the survival time of ischemic penumbra in patients with acute ischemic stroke is the blood supply of collateral artery. The status of cerebral collateral circulation is closely related to the development of acute ischemic stroke, the recanalization rate of endovascular treatment and the clinical prognosis. This article mainly summarizes the types, characteristics, imaging assessment method of cerebral collateral circulation and its application in emergency mechanical thrombectomy of acute ischemic stroke.

【**Key words**】 Collateral circulation; Stroke; Brain ischemia; Thrombectomy; Review
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2015年，*N Engl J Med*相继公布MR CLEAN[1]、EXTEND - IA[2]、ESCAPE[3]、SWIFT PRIME[4]和REVASCAT[5]等大型多中心前瞻性随机对照临床试验结果，进一步证实机械取栓治疗颅内大动脉急性闭塞安全、有效。然而，根据2018年*JAMA*公布的最新数据，仍有26%～49%的患者血管再通后失败[6]。研究显示，良好的侧支循环可以延长急性缺血性卒中机械取栓的治疗时间窗，同时可增加血管再通率和降低脑出血风险[7-8]，提示侧支循环、梗死灶体积等因素与患者长期预后密切相关[9-11]。笔者拟对侧支循环评估在机械取栓治疗急性缺血性卒中的应用进展进行概述，进一步了解侧支循环评估在诊断与治疗中的价值和必要性。

一、颅内侧支循环类型与特点

颅内侧支循环系指脑血管严重狭窄或闭塞时，血流通过扩大的或新开放的侧支到达狭窄或闭塞血管之远端，使缺血区域脑血流量（CBF）得到不同程度的恢复，是颅内循环代偿机制之一，可增加脑卒中后缺血半暗带区供血，在急性缺血性卒中血管再通和预后评价中发挥重要作用。

广义的侧支循环包括动脉侧支循环和静脉侧支循环，其中以动脉侧支循环更受关注，根据开放层次可分为3级，即初级侧支循环、次级侧支循环和三级侧支循环。初级侧支循环即Willis环，为颅内最重要的侧支循环途径，主要沟通双侧大脑半球和前后循环，在缺血早期发挥代偿作用。次级侧支循

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作者单位：300192 天津市第一中心医院放射科（王健、夏爽），神经外科（冯学泉）；300071 南开大学医学院研究生院2018级（祁子禹）
通讯作者：冯学泉，Email：fengxuequan@126.com

环系指相对于Willis环的较小的血管吻合支，以眼动脉和软脑膜侧支循环为主，当Willis环代偿无法满足脑组织供血时，次级侧支循环通路即发挥作用。眼动脉是重要的次级侧支，沟通颈内动脉（ICA）与颈外动脉（ECA），主要与上颌动脉分支如脑膜中动脉、眶下动脉等相交通构成侧支循环通路，如果颈内动脉在眼动脉发出前即出现慢性严重狭窄或闭塞，颈外动脉可经眼动脉逆流供应颈内动脉；软脑膜侧支主要存在于颅内大动脉供血区邻近部位，如大脑前动脉（ACA）和大脑中动脉（MCA）供血区边缘部位、大脑中动脉与大脑后动脉（PCA）供血区边缘部位，目前有关软脑膜侧支循环开放的决定因素尚未确定，推测可能与患者基础血糖、大脑中动脉近端狭窄或同侧不完整的Willis环等因素有关[12]。三级侧支循环则为新生血管，包括血管发生、血管新生、动脉形成共3种途径；当次级侧支循环代偿仍无法满足脑组织供血时，新生血管即成为最终的侧支循环，但由于三级侧支循环的建立需要一定时间，在急性缺血性卒中机械取栓中难以发挥有效作用。

二、侧支循环与缺血性脑血管病之间的关系

1. 侧支循环可以减少甚至预防缺血性卒中的发生　在上述侧支循环代偿机制中，首先开放的是Willis环，即前交通动脉（ACoA）和后交通动脉（PCoA），而Willis环的形态和变异程度决定其代偿能力的大小。正常情况下，双侧大脑半球与前后循环的血流压力差相近，前交通动脉和后交通动脉仅作为具有代偿潜力的血管而存在；当局部脑血流量（rCBF）改变时，血流经Willis环重新分配，获得新的血流压力差平衡。对于Willis环较为完整的颈内动脉重度狭窄患者，良好的侧支循环可以有效降低因脑组织低灌注所导致的短暂性脑缺血发作（TIA）或缺血性卒中风险。虽然Willis环为缺血性卒中患者的脑血流重新分配提供了最为重要、最为充分的侧支循环途径，但在临床实践中完全依靠Willis环作为代偿机制的病例较为少见，而以联合次级侧支、软脑膜侧支或其他多种代偿机制的侧支循环方式更为常见。侧支循环建立的类型、速度和数目对梗死灶大小和患者预后具有重要影响。良好的侧支循环可以增加缺血半暗带区的血供，减少或预防缺血性卒中的发生[13-15]。

2. 缺血性脑血管病可促进侧支循环的建立　侧支循环存在于大部分组织器官中，是连接相邻血管的吻合支，遗传因素决定侧支动脉数目和直径[16]。颅内动脉狭窄或闭塞既可能是缓慢进展的过程，亦可能是一种突发事件，颅内动脉闭塞后，侧支循环的代偿程度与Willis环的完整性、有效侧支循环数目密切相关，而动脉闭塞部位、发生速度和发育是否良好等则是决定侧支循环类型、建立速度和代偿程度的重要影响因素[17]。如果颅内动脉狭窄或闭塞发生于Willis环近端且Willis环发育良好，则初级侧支循环开放即可为狭窄或闭塞血管供血区脑组织提供较为充足的血流灌注；若动脉狭窄或闭塞发生于Willis环远端，如大脑中动脉M1段狭窄或闭塞，Willis环则难以发挥其代偿作用，需依靠软脑膜侧支等次级吻合支供血[18]。对于突发性缺血性卒中或直径较粗大的动脉狭窄或急性闭塞，例如房颤栓子脱落阻塞大脑中动脉，由于短时间内无法建立有效的侧支循环，神经功能缺损程度比较严重[19]；反之，动脉狭窄或闭塞呈缓慢进展病程，如动脉粥样硬化性狭窄或闭塞，侧支循环则可伴随动脉粥样硬化性疾病的缓慢进展而逐渐建立并发挥其有效的代偿作用，患者可无明显的低灌注缺血表现，脑组织损害程度亦较轻[20]。

3. 侧支循环的建立顺序　如前所述，缺血性脑血管病的侧支循环通常是由高级至低级发挥其代偿作用的，动脉粥样硬化性疾病即是如此，不同类型脑血管病形成侧支循环的代偿方式不尽相同。例如烟雾病，由于双侧颈内动脉末端呈渐进性闭塞，因此在疾病进展过程中首先形成烟雾状颅底毛细血管网（三级侧支），而后再形成颅内外血管吻合（次级侧支），此类患者对硬脑膜或颞肌贴敷治疗有效，经过一段时间的治疗后即可见血管新生（三级侧支）[21]。这种情况在未经治疗的动脉粥样硬化性闭塞病例中则较为少见[22]，因此，明确不同血管病变的代偿机制对制定个体化手术方案至关重要。

三、侧支循环评价的影像学方法

侧支循环的影像学评价方法分为直接法和间接法，前者主要基于脑血管检查，包括经颅多普勒超声（TCD）、CTA、MRA、数字减影血管造影术（DSA）等；后者则是基于脑组织灌注的检查，如CT灌注成像（CTP）、灌注成像（PWI）、氙气CT（Xe-CT）、PET、SPECT等。

1. 数字减影血管造影术　DSA至今仍是评价颅内侧支循环的“金标准”。目前国际上的大多数临床研究均采用美国介入和治疗性神经放射学学会

(ASITN)/美国介入放射学学会(SIR)制定的血流分级方法对侧支循环进行分级[23]:0级,无侧支血流灌注至缺血区;1级,缓慢的侧支血流灌注至缺血周围区域,伴持续性脑组织低灌注;2级,快速的侧支血流灌注至缺血周围区域,伴持续性脑组织低灌注,但有部分血流灌注至缺血区域;3级,静脉晚期可见缓慢但完全的血流灌注至缺血区域;4级:通过逆行灌注可见快速而完全的血流灌注至整个缺血区域。DSA可动态显示侧支循环的解剖结构和代偿供血范围,并确定颅内动脉狭窄或闭塞部位,DSA联合压颈试验可进一步判断Willis环开放、次级侧支和软脑膜侧支开放程度等。然而,DSA也存在一定局限性。首先,其无法定量评价不同类型代偿模式的血流动力学状态,如无法评价局部脑血流量;其次,需采用高压注射器和一定剂量的对比剂,而对比剂的剂量和压力差异不仅会影响远端血管显影,还可因压力差异而出现逆向充盈,导致假阳性结果;再次,DSA为有创性检查,费用昂贵,故临床应用率较低[24]。

2. CTA和CT灌注成像 CTA是目前临床常用的侧支循环评价方法之一,在评价Willis环解剖变异时具有较高的灵敏度和特异度(均>90%)[25]。CTA包括单相、多相和四维CTA(4D-CTA)。其中,单相CTA可以显示侧支动脉的分布和充盈范围,检查方法简便、快捷,但缺乏时间信息。有研究表明,经单相CTA提示侧支循环不良的患者中有31%不仅临床结局良好,而且多相和动态CTA分别显示侧支循环良好,这是由于侧支循环缓慢的逆向充盈被单相CTA忽略所致[25]。多相CTA和4D-CTA在单相CTA的基础上增加了时间维度,可多相记录对比剂流入和流出血管的全过程,除可显示单相CTA的相关信息外,还可提供侧支充盈速度,后者对确定最终梗死灶体积具有独立预测价值[26];此外,多相CTA还可提供Ktrans值以反映三级侧支循环代偿状态[27];4D-CTA较多相CTA具有更高的时间和空间分辨力,目前多用于预测终末梗死灶体积、脑梗死进展、继发性脑水肿、患者预后等临床结局[28]。CTP是基于中心容积定律,根据脑血流量、脑血容量(CBV)和平均通过时间(MTT)提供血流灌注的定性和定量图像,计算公式为CBF=CBV/MTT,对区分缺血核心区与缺血半暗带区和良性缺血区(即代谢稳定的非临界减少血流区域)有鉴别诊断作用[29]。在制定急性缺血性卒中患者血管再通治疗方案时,CTA可以提供治疗后血流通畅与否的信息,而CTP同时还可以根据脑血流量和平均通过时间提供脑组织再灌注的信息,与CTA相比,CTP可更准确地预测终末梗死灶体积、评价存在梗死风险脑组织的持续生存能力,虽为一种间接评价方式,但具有好的临床应用价值[30]。

3. MRA和灌注成像 MRA评价侧支循环的方式包括时间飞跃MRA(TOF-MRA)和对比剂增强MRA(CE-MRA)等。TOF-MRA通过流入增强效应而突显血流信号,对Willis环近端血管的检测敏感性极高[31],从原始图像上即可分辨出直径为1 mm的血管;而最大密度投影(MIP)可提高其特异性。MRA评价前交通动脉和后交通动脉的灵敏度分别为89.2%和81.3%[32],但与血流动力学有关的因素均可影响成像质量,因此TOF-MRA无法清晰显示血流速度较慢的次级和三级侧支,准确性较差[33]。CE-MRA通过注射顺磁性对比剂以显示血管走行,检查过程中无血流造成的伪影,呈均衡血流信号,有利于颅内小血管如软脑膜侧支的显示,与侧支循环不良的患者相比,侧支循环良好的患者达峰时间(TTP)延迟程度不十分明显,而且缺血区脑血容量相对正常或仅轻度增加[34]。目前有关PWI侧支循环的分级标准尚未达成共识,概率加权模型主要是通过灌注延迟(达峰时间16~22秒)以确定侧支循环状态[35]。采用动态磁敏感对比增强灌注成像(DSC-PWI)进行数据后处理有助于观察侧支循环状态[36],采用对比剂示踪的后处理和可视化技术可鉴别侧支血流与正常血流,并快速显示侧支动脉[37];数字减影灌注成像(DS-PWI)可用于侧支循环分级,有助于发现侧支循环开放程度与脑梗死进展的相关关系[38]。上述检测方法均可直接与扩散加权成像(DWI)和PWI图像信息进行对比,无需经传统的血管造影图像对侧支循环进行评价。

4. 经颅多普勒超声 通过频谱波形,以及血流方向、速度、强度的变化提供不同病理状态下的脑血流信息,可以较好地提供前交通动脉和后交通动脉血流量、流速等参数,但无法对次级和三级侧支循环进行评价。TCD成像质量受多种因素的影响,如操作技术、骨窗厚度等,且无法完整提供Willis环信息,亦不能对次级和三级侧支循环代偿功能进行评价[39],对侧支循环的评价作用十分有限,但作为一项简便易行、费用低廉、可重复操作、能够提供脑血流信息的无创性检查方法,仍可用于评价缺血性

卒中患者侧支循环代偿能力的初步筛查。

四、侧支循环评估用于急性缺血性卒中机械取栓

1. 预判急诊机械取栓疗效　初级和次级侧支循环代偿程度对急性缺血性卒中患者的脑血流代偿能力具有代表意义，因此是一重要的个体化治疗时间窗。有资料显示，侧支循环良好的患者血管再通治疗后血管完全再通比例为42%，而侧支循环不良者仅为14%[40]。机械取栓后血管再通与否也是判断患者预后的重要因素，包括侧支循环评估和改良脑梗死溶栓血流分级（mTICI）。Gerber等[41]采用CTA图像对前循环闭塞患者血管内治疗后的软脑膜侧支代偿能力进行分级，结果显示，mTICI评分与临床结局（成功再灌注）显著相关，而侧支代偿能力与临床结局无关联性；进一步分析二者对临床结局的预测价值，提示侧支循环分级为临床结局强有力的预测因子（$OR=9.690$），但mTICI评分较侧支循环评估的预测能力更高（$OR=26.500$）。

2. 指导急诊机械取栓的病例筛选　血管内机械取栓治疗须严格掌握手术适应证，以免因术后严重脑水肿或脑出血等并发症而致手术失败。目前，CT和MRI为筛选血管再通治疗适应证的首选方法。扩散和灌注成像评价脑卒中进展研究（DEFUSE）首次提出“恶性征象（malignant profile）”的概念，定义为基线DWI体积＞100 ml或达峰时间延迟＞8秒的严重脑缺血患者为机械取栓治疗的禁忌证，存在恶性征象的患者，由于在疾病进展过程中梗死灶体积可增加且再灌注率进一步降低，因此术后极易发生症状性颅内出血或预后不良[42-43]。而DEFUSE2研究则将PWI体积＞85 ml且达峰时间延迟＞8秒作为临界值，凡达到“临床界值”的患者即被视为术后发生颅内出血的高风险人群，预后不良[44]。DEFUSE系列研究提出的“目标mismatch”概念，主要用于筛选血管再通治疗的适应证”，定义为：（1）低灌注区（达峰时间＞6秒）体积/DWI缺血核心区体积≥1.80，绝对值≥15 ml。（2）DWI缺血核心区体积≤70 ml。（3）严重低灌注区（达峰时间＞10秒）体积≤100 ml。观察结果表明，与不存在目标mismatch的患者相比，存在目标mismatch的患者，无论是静脉溶栓还是血管内治疗后均较少发生梗死灶体积增加事件，预后良好[44]。与静脉溶栓联合老一代机械取栓装置（Merci碎栓和取栓装置、Penumbra吸栓装置等）相比，静脉溶栓联合支架取栓术后血管再通更为迅速、再通率更高，该项研究支持以PWI图像显示达峰时间＞10秒作为识别严重低灌注区标志的假说[45]。

3. 侧支循环评估的局限性　Nogueira等[46]对存在SWIFT PRIME恶性征象（CTP体积＞100 ml且达峰时间＞10秒）但仍接受血管再通治疗的患者进行预后评价，结果显示再灌注出血风险（4%）和病死率（7%）与对照组差异无统计学意义，提示以SWIFT PRIME恶性征象作为急性缺血性卒中血管内治疗的禁忌证尚存争议。由此可见，目前临床常用的侧支循环评估方法对软脑膜侧支循环的评价存在一定的局限性，而且对评价预后、指导病例筛选也存在不确定性，这种不确定性可能与患者脑组织代谢、局部脑血管侧支循环建立情况、脑区定位等因素有关。

五、展望

血运重建是治疗急性缺血性卒中的重要方法。静脉溶栓、血管内治疗或颅内动脉旁路手术等疗效确切，但哪些患者能从中获益尚无定论，因此评价每例患者的治疗风险-效益比至关重要，侧支循环评估则可为之提供新的思路。目前，神经影像学用于评价侧支循环的临床研究发展十分迅速，随着对侧支动脉结构以及血流动力学、组织代谢和神经元功能变化等检测方法的不断优化，侧支循环影像学评价必将促进缺血性卒中个体化诊断与精准治疗方案和侧支循环研究的发展，并有助于验证增加有效侧支循环的新疗法，甚至从根本上改变急性缺血性卒中的治疗策略。

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