·综述·

急性缺血性卒中血管内治疗研究进展

林育意 谭静 路星辰

【摘要】 急性缺血性卒中发病率、病残率和病死率均较高，是目前对人类危害最严重的疾病之一。血管内治疗已获得临床充分肯定。血管内治疗适应证的选择、治疗时间窗的确定、机械取栓装置的选择对预后至关重要。本文拟对急性缺血性卒中血管内治疗研究进展进行阐述。

【关键词】 卒中； 脑缺血； 血栓溶解疗法； 血管成形术； 综述

Research progress of endovascular therapy for acute ischemic stroke

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【Abstract】 Acute ischemic stroke which has the high mobidity, disability rate and mortality is one of the most serious diseases threatening mankind. Endovascular therapy is difinite. Slection of patient, therapeutic time window and device is closely associated with the prognosis. This paper reviews the issues mentioned above.

【Key words】 Stroke; Brain ischemia; Thrombolytic therapy; Angioplasty; Review

脑卒中是目前对人类危害最严重的疾病之一。全国第三次死因回顾抽样调查和第二次全国残疾人抽样调查资料显示，脑卒中已成为我国国民首位病残和病死原因[1]。在美国，脑卒中是导致终身残疾的首要原因，是第4位病死原因[2]。截至2010年，脑卒中位列全球病残和病死原因的第3和2位[3-4]。虽然近年来脑卒中病死率有所下降，但病残和病死的绝对病例数仍在增加[5]，据世界银行预测，如果不采取有效措施，截至2030年，我国将有31.77×10^6例脑卒中患者[1]。劳动力丧失和医疗负担成为脑卒中生存者、家庭和社会的沉重负担。有效的治疗方法是临床医师不懈追求的目标。

一、急性缺血性卒中静脉溶栓治疗

目前，缺血性卒中是我国脑卒中住院患者的主要类型，占全部脑卒中70%以上[1]。静脉溶栓是经典治疗方法。研究证实，脑卒中静脉溶栓治疗有效，发病后3小时为治疗时间窗[6-7]。1996年，重组组织型纤溶酶原激活物（rt-PA）经美国食品与药品管理局（FDA）批准用于脑卒中静脉溶栓治疗[8]。2008年欧洲协作组急性脑卒中研究Ⅲ（ECASSⅢ）首次将脑卒中静脉溶栓治疗时间窗自3小时延长至4.50小时[9]，并获得临床研究证据的支持[10-11]。

随着临床应用的普及，静脉溶栓治疗的局限性也逐渐凸显。（1）治疗时间窗窄：尽管已将脑卒中静脉溶栓治疗时间窗延长至发病后4.50小时，但在此时间窗内仍有较多患者，特别是偏远地区、交通欠发达地区患者，难以到达有静脉溶栓资质的医院，且此治疗时间窗后不良结局发生率较高。（2）血管再通率低：颈内动脉（ICA）或基底动脉闭塞后静脉溶栓治疗的血管再通率仅为4%～14%，大脑中动脉（MCA）为55%，大脑中动脉M1段闭塞为32%～37%，病残率和病死率均较高[12-13]。（3）易导致脑出血：有文献报道，静脉溶栓治疗后症状性脑出血发生率高达1.7%～2.4%[9,14]。

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二、急性缺血性卒中血管内治疗

1. 血管内治疗的有效性 2013年发表于*N Engl J Med*的3篇关于血管内治疗的随机对照临床试验并未显示血管内治疗较rt-PA静脉溶栓治疗更有优势[15-17]。此后，Singh等[2]对上述3项临床研究进行Meta分析，也得出相同结论。但是他们发现，对于重症脑卒中，血管内治疗效果更佳[2,15-17]。究其原因，可能是血管内治疗尚缺乏大样本多中心随机双盲对照临床试验，也可能与机械取栓装置Merci落后、患者征募缓慢、脑组织再灌注延迟、所纳入病例均质性不一致有关。随着机械取栓装置和取栓技术的进步，血管内治疗的优势逐渐凸显[2,18]，较单纯静脉溶栓治疗效果更佳[19]。两项采用机械取栓装置Stentrievers治疗脑卒中的随机对照临床试验结局均明显改善[20-21]。截至2015年，5项里程碑式前瞻性随机对照临床试验均显示，与静脉溶栓相比，血管内机械取栓治疗近端动脉闭塞性缺血性卒中的治疗时间窗更长、血管再通率更高、临床预后更佳[22-26]。2013和2015年的8项临床研究虽然纳入与排除标准不尽相同[15-17,22-26]，但Badhiwala等[27]对其进行Meta分析后发现，与内科治疗联合rt-PA静脉溶栓治疗相比，急性缺血性卒中患者采用血管内机械取栓治疗能够更好地改善神经功能预后，脑血管造影显示血管再通率更高，且不增加90天内症状性脑出血发生率和各种原因导致的病死率。

2. 血管内治疗患者的选择 Chia等[28]在南澳大利亚的Adelaide西郊进行一项以人群为基础的队列研究，结果显示，在严格[改良Rankin量表(mRS)评分0～1分，发病至入院时间＜3.50小时，梗死灶核心与缺血半暗带区不匹配]和宽松(mRS评分0～3分，发病至入院时间＜5小时)两种标准下，符合血管内血栓切除术(ET)治疗的潜在脑卒中患者约占全部脑卒中患者的7%和13%，宽松标准预测每年符合血管内血栓切除术治疗的潜在患者≤22/10万。2015年，Urra等[29]对纳入前循环大血管闭塞致急性脑卒中8小时内Solitaire FR支架取栓与内科治疗随机对照试验(REVASCAT)的西班牙前循环大血管闭塞性缺血性卒中患者和未纳入该项试验的其他类型脑卒中患者的血管内机械取栓治疗效果进行分析，结果显示疗效无明显差异，表明血管内血栓切除术不仅适用于前循环大血管闭塞性缺血性卒中，还具有更广泛的适应证。如何准确、快速地筛选血管内治疗适应证患者，是所有神经科医师面临的挑战。Alberta脑卒中计划早期CT评分(ASPECTS)是一种采用头部非增强CT扫描快速、简单、可靠、系统化评价脑组织早期缺血性改变的方法[30]。该评分系统中CT检查操作简单、检查时间短、设备普及率高，可以广泛应用于血管内治疗患者的筛查。研究显示，ASPECTS评分＞7分的缺血性卒中患者，动脉或静脉溶栓治疗后预后较好[31-32]。目前，ASPECTS评分广泛应用于选择适合血管内治疗的患者。Goyal等[33]对2015年发表的5项关于血管内治疗的随机对照临床试验进行Meta分析，结果显示，ASPECTS评分优良(7～10分)的患者经血管内治疗后获益明显，而ASPECT评分差(0～6分)的患者经血管内治疗后亦未发现有害证据。Yoo等[34]对荷兰急性缺血性卒中血管内治疗多中心随机对照临床试验(MR CLEAN)进行亚组分析，结果显示，中等梗死灶(ASPECTS评分5～7分)患者经血管内治疗后获益最大，小梗死灶(ASPECTS评分8～10分)患者经血管内治疗联合常规治疗后缺血性卒中复发率增加，大梗死灶(ASPECTS评分0～4分)患者经血管内治疗后是否获益仍不明确，尚待进一步研究。上述研究结论的差异可能是由于CT平扫对急性梗死灶敏感性和精确性均较差[35]；ASPECTS评分应用者之间的异质性较大，约1/3研究者对15%缺血性卒中患者的ASPECTS评分意见不一致[36]，因此，ASPECTS评分用于血管内治疗适应证的选择尚存局限性。研究显示，缺血半暗带血栓检测、CTA原始图像(CTA-SI)有助于选择适合血管内治疗的急性缺血性卒中患者[37]。然而，综合比较CT平扫的简便快捷(可以争取更多时间进行血管内治疗以挽救缺血半暗带)与MRI和CTA等检查(准确性高但检测时间较长)之间的关系，目前尚无除ASPECTS评分外的更好评价方法[38]。

3. 血管内治疗时间窗 脑卒中后应尽可能缩短再灌注时间[19]，普遍认为，再灌注时间延长使临床预后恶化，增加并发症发生率[39]。晚近研究显示，血管内治疗对发病6小时内患者安全、有效[22,24-25]。美国心脏协会(AHA)/美国卒中协会(ASA)制定的急性缺血性卒中血管内治疗指南[40]建议，应于发病6小时内行血管内治疗。《急性缺血性卒中血管内治疗中国指南2015》[41]推荐，血管内机械取栓治疗发病6小时内的急性前循环大动脉狭窄性缺血性卒中，如果发病4.50小时内，可在足量静脉溶栓基础上实施血管内机械取栓治疗。但是发病6小时后行

血管内治疗是否获益尚存争议。理论上讲，如果侧支循环良好、可挽救的缺血半暗带体积足够大，即使延长治疗时间窗也可以获益。Jovin等[26]进行的REVASCAT试验纳入发病8小时内的前循环大血管闭塞性缺血性卒中患者，血管内机械取栓可显著降低脑卒中后残疾程度，增加生活自理[mRS评分0~2分]比例，且与单纯内科治疗相比，症状性脑出血发生率和病死率差异无统计学意义。Saver等[42]的Meta分析显示，脑卒中发病2小时内行血管内治疗联合内科治疗获益最大，发病后7.30小时已无明显获益。Goyal等[23]的小梗死灶和前循环近端闭塞性缺血性卒中血管内治疗并强调最短化CT扫描至再通时间(ESCAPE)试验将纳入时限延长至发病12小时内，同样发现血管内治疗可以明显改善患者功能预后并降低病死率。Lansberg等[43]的前瞻性多中心队列研究——扩散和灌注成像评价脑卒中进展2(DEFUSE2)研究显示，对于发病12小时内灌注成像(PWI)-扩散加权成像(DWI)不匹配的缺血性卒中患者，血管内再灌注成功与功能和影像学预后改善(发病至接受再灌注治疗时间)无时间依赖性。应注意的是，加拿大脑卒中治疗指南[44]建议，发病6小时内血管内治疗效果最佳，最多可延长至发病12小时内。从个体水平看，发病超过6小时的缺血性卒中患者仍有可挽救的缺血半暗带，可采用多模式影像学检查，如CT灌注成像(CTP)、CTA、DWI和PWI筛选适合血管内治疗的患者，但是此类患者能否从急性缺血-再灌注中获益，尚待进一步随机对照临床试验的验证[40]。

4. 血管内治疗装置的选择　目前，血管内取栓装置根据取栓方法可以分为两种类型，一种以Merci(美国Concentric Medical公司)取栓系统和Penumbra(美国Penumbra公司)吸栓系统为代表，一种以Solitaire(美国EV3公司)和Trevo(美国Stryker公司)可回收支架取栓系统为代表。支架种类、型号、形状和物理性质对临床实践和预后结局的影响尚不明确，因此，机械取栓装置的选择也尚无定论。有5项随机对照临床试验证实可回收支架取栓系统的优良效果[22-26,33]。Dippel等[45]对MR CLEAN试验中不同取栓装置的临床结局进行分析，发现Solitaire和Trevo支架取栓装置的效果最佳，Catch(美国Guidant公司)、Lazarus(美国Lazarus Effect公司)、Merci、Penumbra、Revive(美国Johnson & Johnson公司)等装置取栓后7天和3个月病死率和蛛网膜下隙出血发生率均明显高于Solitaire和Trevo支架取栓装置，而二者的临床结局、神经修复、血管再通率、最终梗死灶面积和病死率差异则无统计学意义。Mendonça等[46]的前瞻性临床研究对前循环闭塞后Solitaire和Trevo支架取栓装置的疗效进行比较，结果显示，两种装置取栓后血管再通率均较高(60%对77%，$P=0.456$)，且临床、影像学和功能结局差异均无统计学意义；然而由于样本量较小(仅33例)，该项研究结论尚待进一步证实。Grech等[47]对2010–2013年发表的20篇关于血管内机械取栓装置的临床研究(包括Solitaire支架17篇、Trevo支架3篇)进行Meta分析，结果显示，Solitaire和Trevo支架取栓后血管再通率均>80%，二者功能结局、病死率和症状性脑出血发生率差异均无统计学意义。因此认为，第一种类型的吸栓系统疗效未能达到预期，而第二类型的可回收支架取栓系统疗效达到预期，表现卓越。

综上所述，血管内治疗已获得临床充分肯定，中国神经外科医师、相关学者和科研机构也紧随时代步伐在该领域作出大量工作[48-49]。随着相关设备和技术的迅速发展，相信在不久的将来，血管内治疗必将得到进一步的完善和普及。

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Wernicke脑病

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Wernicke´s encephalopathy

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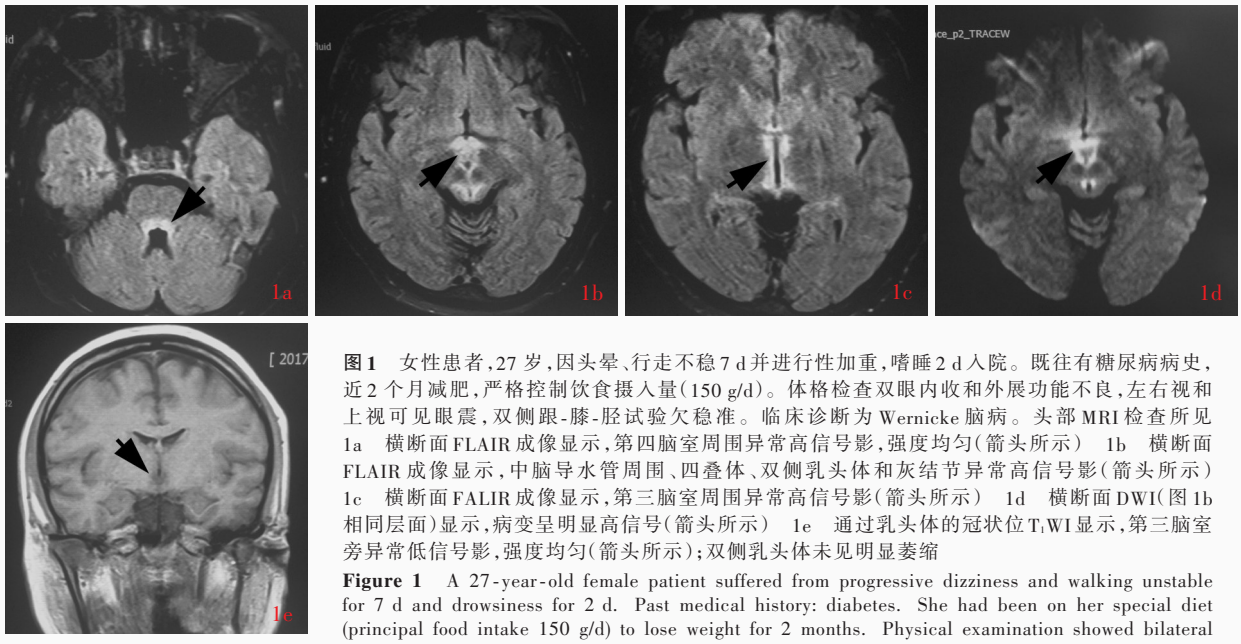

图1 女性患者,27岁,因头晕、行走不稳7 d并进行性加重,嗜睡2 d入院。既往有糖尿病病史,近2个月减肥,严格控制饮食摄入量(150 g/d)。体格检查双眼内收和外展功能不良,左右视和上视可见眼震,双侧跟-膝-胫试验欠稳准。临床诊断为Wernicke脑病。头部MRI检查所见 1a 横断面FLAIR成像显示,第四脑室周围异常高信号影,强度均匀(箭头所示) 1b 横断面FLAIR成像显示,中脑导水管周围、四叠体、双侧乳头体和灰结节异常高信号影(箭头所示) 1c 横断面FALIR成像显示,第三脑室周围异常高信号影(箭头所示) 1d 横断面DWI(图1b相同层面)显示,病变呈明显高信号(箭头所示) 1e 通过乳头体的冠状位T_1WI显示,第三脑室旁异常低信号影,强度均匀(箭头所示);双侧乳头体未见明显萎缩

Figure 1 A 27-year-old female patient suffered from progressive dizziness and walking unstable for 7 d and drowsiness for 2 d. Past medical history: diabetes. She had been on her special diet (principal food intake 150 g/d) to lose weight for 2 months. Physical examination showed bilateral ocular palsy, nystagmus in the side view (left and right) and front view. She could not complete both heel-knee-tibia test correctly and stalely. She was clinically diagnosed as having Wernicke´s encephalopathy. Axial FLAIR image through pons revealed an abnormal heterogeneous hyperintensity mainly located at the tegmental part of pons around the forth ventricle (arrow indicates, Panel 1a). Axial FLAIR image through midbrain showed multiple heterogeneous hyperintensity lesions distributed symmetrically on the left and right sides located at periaqueductal area, corpus quadrigemina, bilateral mammillary bodies and tuberculum cinereum (arrow indicates, Panel 1b). Axial FLAIR image through thalamus showed abnormal hyperintensity located around the third ventricle (arrow indicates, Panel 1c). Axial DWI located at the same level as 1b revealed abnormal hyperintensity lesions (arrow indicates, Panel 1d). Coronal T_1WI through mammillary body showed markedly heterogeneous slightly hypointensity in bilateral wall of the third ventricle (arrow indicates). There was no significant atrophy of bilateral mammillary bodies (Panel 1e).

Wernicke脑病是维生素B_1缺乏导致的代谢性脑病,1881年由Wernicke首先描述,1940年Campbell和Russell提出其诱因是维生素B_1缺乏。该病系维生素B_1缺乏致特定区域神经细胞能量代谢障碍所致,呈急性或亚急性起病,临床主要表现为眼外肌瘫痪、共济失调和意识障碍,最常见于慢性酒精中毒和妊娠性呕吐;非维生素B_1缺乏性Wernicke脑病系转酮醇酶(*TK*)基因缺陷所致。MRI对早期诊断和疾病分期有重要价值,是首选影像学方法。典型特征为特定部位出现特定分布的病变,特定部位包括第四脑室旁(脑区被盖和中脑顶盖,图1a)、中脑导水管周围、乳头体、四叠体(图1b)、第三脑室侧壁(丘脑内侧,图1c),其中乳头体最易受累,也可发生于延髓、小脑齿状核、红核、中脑顶盖、尾状核和大脑皮质等少见部位;特定分布指病变分布呈对称性。急性期,病变区神经细胞可见细胞毒性水肿和血管源性水肿伴神经胶质和巨噬细胞增生,T_2WI、FLAIR成像(图1a~1c)和DWI(图1d)呈高信号,T_1WI呈稍低信号(图1e);亚急性期,以血管源性水肿为主,脑室旁白质可见缺血性脱髓鞘改变,脑干长T_2信号与神经纤维网络海绵样变性相关,随着病情进展,血-脑屏障破坏、血管外膜损害,增强扫描病变呈明显强化,治疗后MRI异常信号和强化可以逆转甚至消失;慢性期,随着神经细胞缺失,上述病变范围缩小,乳头体和中脑顶盖可见萎缩性改变,相邻第三和第四脑室扩大。应注意与多发性硬化、视神经脊髓炎谱系疾病,病毒性脑炎累及脑干、脑血管病等相鉴别。

(天津市环湖医院神经放射科韩彤供稿)