·述 评 Comment·

脑缺血性疾病血管内治疗的现状和展望

李明华, 赵俊功

脑血管疾病是死亡率第三位、致残率第一位严重危害人类健康的疾病,而缺血性卒中占脑血管疾病的 55% ~ 80%。临床上缺血性卒中的原因主要是脑动脉血栓形成所致的急性梗死和各种原因引起的颅颈动脉管腔的狭窄引起的脑缺血、缺氧性改变。在急性脑梗死中,动脉粥样硬化斑块脱落、心源性栓子脱落是主要原因,而动脉粥样硬化、纤维肌发育不良、以及动脉炎等均可以引起颅颈动脉管腔的狭窄,其中,动脉粥样硬化是主要的原因。

诊断技术的提高和介入治疗新材料的不断推出,为缺血性脑血管病血管内治疗开辟了新的领域。已有的研究结果表明,急性期脑梗死的动脉内溶栓,因闭塞动脉开通率提高,显著降低了缺血性脑血管病的致残率和致死率 狭窄段动脉的支架成形术,改善病变血管远端的供血,可预防缺血性卒中的再次发生。因此,急性期脑梗死的动脉内溶栓和颅颈动脉狭窄段的支架成形术在国内外都陆续开展起来。

如何遴选合适的急性脑梗死患者接受溶栓治疗、降低溶栓的并发症是国内外学者共同追求的目标。CT 灌注成像、MR 弥散成像(DWI)、MR 灌注成像(PWI)和无创性的血管成像技术(包括 CEMRA、CTA),在证实并图解脑缺血的存在及其部位和原因、评估缺血组织的生存能力和可逆性、预测治疗结果等方面都发挥了重要的作用。例如,PWI 与 DWI 的不重叠区表示缺血半影区的理论,为临床溶栓治疗筛选病例提供了指导性意见。然而这种不重叠模型是建立在以下 2 种假设之上:①DWI 上异常信号区域的边缘将梗死的中心(不可逆梗死脑组织)与半影区分割开来;②PWI 的异常信号区域的边缘将半影区与无缺血的脑组织分割开来。最近的研究表明:DWI 上异常信号区域内包含半影区,PWI 的异常信号区域包含良性血流减少(不会发生脑梗死的危险),并非都是半影区。这些研究结果对"PWI 与 DWI 的不重叠区预示缺血半影区的理论"提出了挑战。国外学者已运用 DWI、PWI 的多参数模型对脑缺血不同区域进行定量化分析,来弥补不重叠模型的不足。但这些参数的敏感度和特异度缺乏统一的标准。本期所刊出的"大鼠急性脑梗死后不同区域扩散和灌注成像的变化特点"一文,运用半定量化分析的方法来评价急性脑梗死后有活性脑组织,亦是一种积极的尝试。

阻碍急性脑梗死溶栓治疗得以广泛开展的原因是,只有少数患者能在发病 3 h 内接受溶栓治疗,即使在发达国家也只有 3% ~ 5%。对发病超过 3 h 的患者再进行溶栓治疗,脑出血的发生率大大增加。其机制是脑毛细血管内皮细胞紧密连接开放,细胞外间质(ECM)的溶解,星形胶质细胞足板肿胀与 ECM 脱离。而 ECM 的溶解所引起的血-脑脊液屏障结构的破坏是引起脑出血的主要原因。研究表明,血管舒张素,血管内皮生长因子(VEGF)、基质金属蛋白酶(MMPs)、黏附分子、血小板活化因子、自由基、一氧化氮都参与 ECM 的溶解,甚至溶栓药物 rt-PA 也参与 ECM 的溶解和重塑。为了使更多的急性脑梗死患者能从溶栓治疗中获益,采取积极的措施降低脑出血的发生,对发病超过 3 h 的患者进行溶栓治疗——延长溶栓时间窗,将是有效的途径。国外学者通过机械溶栓、减少 rt-PA 的用量(单纯动脉途径)、应用 7E3F(ab')$_2$ 降低血小板聚集、运用 MMPs 抑制剂 BB-94 或 BB-1101 以及红细胞生成素等对发病超过 3 h 的急性脑梗死进行溶栓,降低了梗死体积,改善了神经功能,脑出血或出血转化的发生率没有显著提高。我们课题组,运用人体白蛋白和硫酸镁作为神经保护药物,对发病 6 h 内的大鼠进行溶栓治疗,也同样减轻了缺血脑组织的损害程度,没有出现脑出血。当然,溶栓后脑出血的发生是多环节、多因素共同作用的结果,单纯某一种药物难以从根本上解决问题。

可以预见的是,通过 CT 或 MRI 的半定量、定量

作者单位:200233 上海交通大学附属第六人民医院介入影像科
通讯作者:李明华

[1] Department of Interventional and Diagnostic Radiology, Affiliated Sixth People's Hospital, Shanghai Jiaotong university
Corresponding author: LI Ming-hua

参数结合 PWI/DWI 的不重叠模型，而不是单纯依靠发病时间来遴选溶栓治疗的患者，在神经药物的干预下，采用机械溶栓或(和)动脉溶栓，将是未来急性脑梗死溶栓治疗的趋势。

在保护伞的帮助下，降低了支架放置过程中斑块脱落而引起远端血管栓塞的风险，使得颈动脉狭窄支架成形术受到了前所未有的关注。在美国、欧洲，颈动脉狭窄支架成形术成为颈动脉内膜剥脱术的主要替代方法。专用颅内支架(APPLO)的问世，由于支架的柔顺性提高，径向支撑力改善，大脑前动脉、大脑中动脉、大脑后动脉主干和椎基底动脉的狭窄，支架均容易到达和通过，同时贴壁性好，使得颅内动脉狭窄支架植入的范围不断拓展和延伸。

值得关注的是，支架植入后，会有一定比例的患者发生近期、远期的再狭窄。虽然国内外学者和研究机构为此付出了不少的努力，但效果不尽如意。所以，当前和今后的一段时间，支架植入的主要问题之一，是如何严格把握适应证、提高效益/风险比。根据我们的经验，通过无创性的血管成像(CTA 或 CEMRA)，了解病变血管的部位和程度，在尽可能的情况下，运用 CT 灌注成像或 MR 灌注成像并结合临床，来判定该病变血管是否为责任血管，是严格把握适应证，提高效益/风险比的较为合理的操作流程。当然，随着 MRI 线圈的改进，信噪比的提高，对颈内动脉甚至颅内动脉易损斑块的准确判定，将会使更多的患者能及时施行支架成形术而受益。

(收稿日期：2005-07-26)

Current status and outlook of endovascular therapy for cerebral ischemic diseases　*LI Ming-hua, ZHAO Jun-gong. Department of Interventional and Diagnostic Radiology, Shanghai Sirth People's Hospital Affiliated Shanghai Jiaotong University, Shanghai* 200233, *China*

With the third mortality and the first criple morbidity, cerebral vascular diseases pose great threat to human health, among which ischemic stroke accounts for 55% to 80%. Clinically, the main reasons for ischemic stroke are thrombosis in cerebral arteries resulting in acute cerebral infarction, and stenosis of intracranial and carotid arteries with cerebral ischemic and hypoxic changes. The major causes for acute cerebral infarction are the defluvium of artherosclerosic plaques, cardiogenic emboli, artherosclerosis, fibromyo-dysplasia and arteritis causing stenosis of intracranial and carotid arteries, with artherosclerosis as the most severe cause.

Improvement of diagnostic technology and increasing advent of new materials for intervention has created a new era for endovascular therapy of cerebral ischemic diseases. Current research findings have shown that endovascular thrombolysis in acute stage of cerebral infarction can acclerate the rate of re-canalization of occluded arteries and greatly decrease the morbidity and mortality of cerebral ischemic vascular diseases. Stenting of arterial stenosis can the improve of blood supply distal to the lesion, prevent recurrent cerebral ischemic stroke. As a result, endovascular thrombolysis for acute cerebral infarction and stenting for intracranial and carotid arterial stenosis are booming both at home and abroad.

Proper selection of patients of acute cerebral infarction for endovascular thrombolysis with less complications could be achieved through CT perfusion, MR Perfusion-Weighted Image (PWI) and Diffusion-Weighted Image (DWI); non-invasive vascular imaging technology including CEMRA and CTA for confirming and demonstrating the sites and causes of cerebral ischemia; and furthermore for evaluating the survival ability and reversibility of ischemic tissues and predicting prognosis etc. For example, the mismatch area on PWI and DWI means the ischemic penumbra provides instruction for clinical selection of patients for thrombolysis. And this mismatch model is based on two hypothesis 1) the borderline of the abnormal signal area on DWI separating the penumbra (central infarction) from non-ischemic tissue, 2) the borderline of the abnormal signal area on PWI separating the penumbra (half-shadow area) from non-ischemic tissue. However, recent research has found that both the abnormal signal areas on DWI and PWI are not all belonging to penumbra. The abnormal signal area on DWI contains ischemic penumbra and the abnormal signal area on PWI includes benign decrease of blood flow which will not result in cerebral infarction. These findings challenge the theory that the mismatch area on DWI and PWI means ischemic penumbra. Scholars from abroad have already applied multi-parameter models of DWI and PWI to quantitatively analyze different cerebral ischemic

areas for complementing the mismatch models. But the parameters still lack of common standards in sensitivity and specificity. The publishing of this edition Characteristics of Diffusion- and Perfusion-Weighted MRI in Different areas of acute stroke in a rat model is an aggressive attempt with a method of semi-quantity to evaluate active cerebral tissue existing in acute cerebral ischemia.

The obstacle in thrombolysis for acute cerebral infarction lies in the fact that only a small number of patients can have access to thrombolysis within 3 hours of onset and only 3%-5% of patients have this oportunity even in developed countries. Hemorrhage rate will increase greatly in patients accepting thrombolysis beyond 3 hours of onset, whose mechanism lies in the opening-up of the tight junction between vascular endothelia, the dissolving of extracellular matrix (ECM), and the swelling of the pedal plates of astrocytes and their detachment from ECM. Dissolving of ECM resulted in the destruction of blood-brain-barrier acts as the major cause of cerebral hemorrhage. It has been shown that angiotensin, vascular endothelial growth factor (VEGF), matrix metalloproteinase (MMPs), adhesion molecules, platelet activating factor, free radicles and nitrogen monoxidum all play a part in the dissolving of ECM. And even thrombolytic drug rt-PA participates in the dissolving and re-shaping of ECM. In order to benefit more patients of acute cerebral infarction with thrombolysis, aggressive measures should be taken to lower the hemorrhagic complication rate and the time window of thrombolysis should be effectively prolonged for patients with cerebral infarction beyond 3 hours. Scholars abroad have treated acute cerebral infarction beyond 3 hours of onset by using mechanic thrombus-disrupting, lowering rt-PA dose administered with only intra-arterially, applying 7E3F $(ab')_2$ to decrease the aggregation of platelet and administering MMPs inhibitors BB-1101 and erythropoietin, and succeeded in decreasing the infarction volume and improving the neurological function without increasing cerebral hemorrhagic complication or hemorrhagic transforming rate. Our research team also administered albumin and magnesium sulfate as neurological protection drug to treat rat infarction model within 6 hours of onset resulting with the same effect of decreasing the damage of ischemic cerebral tissue and without hemorrhagic complication. It is certain that hemorrhagic complication in thrombolysis is a result of multiple factors with no single drug being able to solve the problem.

It is predictable that, based on semi-quantitative or quantitative parameters of CT or MRI in conjunction with PWI/DWI mismatch model rather than simply on the onset time of infarction for proper selection of patients of cerebral infarction, mechanic thrombus-disruption and/or intra-arterial thrombolysis together with intervention of neurological protection drug will be the trend for treating acute cerebral infarction in the future.

The protection umbrella decreases the danger of distal arterial embolism caused by defluvium of artherosclerosic plaques in the process of stent implantation resulting the unprecedented attention for carotid arterial angioplasty with stent placement. In the United States and Europe, stenting of carotid arterial stenosis has become a main alternative to carotid endarterectomy. The invention of customized intracranial stent APPLO has increasingly expanded the range of stenting for intracranial arterial stenosis because of easy manupulation to reach and pass through the stenosis of the anterior, middle, posterior cerebral and vertebrobasilar arteries with its increased pliancy, improved radial support and good adherence.

It is noteworthy some of patients will have re-stenosis shortly or long after stent implantation and even after certain management but without a satisfactory result. As a consequence, the main problem with stent implantation recently and for some time in the future will be how to create proper indications and increase the ratio of benefit to danger. We usually apply non-invasive vascular imaging like CTA or CEMRA to demonstrate the location and degree of stenosis, and utilize CT perfusion or MR perfusion image, if possible, in conjunction with clinical symptoms to determine the responsible arteries. Of course, with the improvement of MRI helix of wire and signal-noise ratio will bring us a precise evaluation of hazardous plaques in carotid and even intracranial arteries. An increasing number of patients will be benefitial from timely stent implantation. (J Intervent Radiol, 2005, 14:449-451)

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作者： 李明华， 赵俊功， LI Ming-hua， ZHAO Jun-gong
作者单位： 200233,上海交通大学附属第六人民医院介入影像科
刊名： 介入放射学杂志 ISTIC PKU
英文刊名： JOURNAL OF INTERVENTIONAL RADIOLOGY
年，卷(期)： 2005，14(5)
被引用次数： 2次

引证文献(2条)

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