DOI:10.16781/j.0258-879x.2022.01.0009

· 专题报道 ·

大血管闭塞急性缺血性脑卒中超时间窗机械取栓研究现状

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［摘要］ 血管再通治疗是大血管闭塞急性缺血性脑卒中（AIS-LVO）最主要的治疗方式。研究证实AIS-LVO机械取栓的明确时间窗为发病6 h内，对于发病6～24 h或超过24 h接受机械取栓的患者筛选仍存争议。本文对发病或末次正常时间为6～24 h的超时间窗AIS-LVO患者和超出24 h的超晚期AIS-LVO患者的机械取栓治疗现状进行总结，并分析延长取栓时间窗的可行性和评估策略。

［关键词］ 急性缺血性脑卒中；超时间窗；大血管闭塞；机械取栓术
［中图分类号］ R 743.3　［文献标志码］ A　［文章编号］ 0258-879X(2022)01-0009-06

Mechanical thrombectomy for acute ischemic stroke with large vessel occlusion beyond time window: current status

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［**Abstract**］ Vascular recanalization therapy is the major treatment strategy for acute ischemic stroke with large vessel occlusion (AIS-LVO). Time window for mechanical thrombectomy has been proven to be within 6 h after stroke onset. Screening of patients who are to undergo mechanical thrombectomy 6-24 h or beyond 24 h after onset remains controversial. In this review, we summarize the current status of mechanical thrombectomy in AIS-LVO patients with extended time window of 6-24 h or beyond 24 h, and analyze the feasibility and evaluate the strategies for extending the time window of thrombectomy.

［**Key words**］ acute ischemic stroke; beyond time window; large vessel occlusion; mechanical thrombectomy
［Acad J Sec Mil Med Univ, 2022, 43(1): 9-14］

脑卒中是世界范围内引起死亡与成年人群残疾的首要病因[1]。随着治疗手段的改进，高收入国家的脑卒中死亡率逐年下降，然而中低收入国家脑卒中的疾病负担依旧呈现增高的趋势[2]。脑卒中是发展中国家人群继冠状动脉性心脏病后导致死亡与残疾的第2位病因，是我国成年人群死亡、残疾的第1位病因，其中缺血性脑卒中约占所有脑卒中的3/4[3]。

机械取栓是大血管闭塞急性缺血性脑卒中（acute ischemic stroke with large vessel occlusion，AIS-LVO）最主要的治疗方式[4]，多项研究证实了发病6 h内机械取栓治疗达到血管成功再通对于AIS-LVO的临床有效性[5-7]。DAWN和DEFUSE 3研究将机械取栓治疗的时间窗从发病6 h内延长至24 h，然而，机械取栓仍然是严格时间依赖性的治疗方式，血管越早再通患者获益越明显[6,8]。随着神经影像学评估技术的发展，超6 h时间窗的缺血性脑卒中患者若计算机断层扫描灌注成像（computed tomography perfusion，CTP）评估存在显著缺血半暗带时仍可从机械取栓治疗获益[9]，那么，超出24 h时间窗且CTP评估存在显著缺血半暗带的缺血性脑卒中患者能否从机械取栓中获

［收稿日期］ 2021-09-20　［接受日期］ 2021-10-26
［基金项目］ 中国脑卒中高危人群干预适宜技术研究及推广项目（GN-2020R0008），上海市扬帆计划（20YF1448000），上海市临床重点专科项目（shslczdzk06101），海军军医大学（第二军医大学）长海医院青年启动基金（2018QNA007）. Supported by Project of Research and Application of Effective Intervention Techniques for High-Risk Stroke Population of China (GN-2020R0008), Shanghai Sailing Program (20YF1448000), Shanghai Municipal Key Clinical Specialty Project (shslczdzk06101), and Youth Initial Fund of Changhai Hospital of Naval Medical University (Second Military Medical University) (2018QNA007).
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益？本文对发病或末次正常时间为6～24 h的超时间窗AIS-LVO患者和超出24 h的超晚期AIS-LVO患者的机械取栓治疗现状进行总结，并分析延长取栓时间窗的可行性和评估策略。

1　超时间窗AIS-LVO患者的流行病学数据

缺血性脑卒中患者的机械取栓治疗按发病时间分为早期（≤6 h）、晚期（＞6～24 h）和超晚期（＞24 h）取栓[6]，目前认为超过6 h取栓为超时间窗取栓。AIS-LVO患者中超时间窗患者的占比并不低，一项回顾性研究中，447例发病24 h内就诊的患者中45.5%就诊时间为发病6～24 h[10]。在临床实践中，有相当比例的超时间窗取栓患者可能因过于严格的筛选标准而丧失取栓机会，统计数据显示因发病时间不明确、就诊晚而丧失取栓机会的患者比例可达40%[11-13]。目前大部分超时间窗研究集中于发病6～24 h取栓，而发病24 h后机械取栓的研究多为个案报道（表1）[4,7,14-26]。

一项单中心回顾性研究收集分析了2 667例AIS-LVO患者资料，发现发病6～16 h的患者占17%，而将时间窗延长至6～24 h该比例上升到30%；1/3的AIS-LVO患者于发病6 h内就诊，发病6～24 h就诊且符合DAWN取栓标准的患者仅占5.7%，而通过联合DAWN和DEFUSE 3研究标准化取栓适应证后发现符合取栓标准的患者占比上升到9.2%，这意味着严格的取栓标准可能导致潜在获益患者丧失取栓机会[15]。DAWN研究筛选标准：（1）距末次正常时间为6～24 h；（2）年龄＜80岁的患者若美国国立卫生研究院卒中量表（National Institutes of Health stroke scale，NIHSS）评分≥10分则核心梗死体积＜31 mL，若NIHSS评分≥20分则核心梗死体积＜51 mL；（3）年龄≥80岁的患者NIHSS评分≥10分且核心梗死体积≤20 mL[7]。DEFUSE 3筛选标准：（1）距末次正常时间为6～16 h；（2）年龄≤90岁且NIHSS评分≥6分；（3）核心梗死体积＜70 mL且缺血体积/梗死体积＞1.8[7]。

2　发病6～24 h的超时间窗AIS-LVO机械取栓治疗是安全、有效的

发病6～24 h、经CTP评估的AIS-LVO患者可机械取栓治疗中获益。一项纳入10项机械取栓相关随机对照试验（randomized controlled trial，RCT）研究的meta分析提示，相较于保守治疗，发病6 h内机械取栓可显著降低90 d死亡率（15.0% vs 18.7%，*RR*＝0.81），发病6 h后机械取栓的患者同样临床获益（*OR*＝0.76）[6]。MR CLEAN研究中，106例（3.2%）患者发病超过6.5 h取栓且其中80%的患者未经CTP筛选，这部分患者的侧支代偿能力更好，且临床预后良好率与时间窗内取栓治疗的患者差异无统计学意义（43.3% vs 40.5%，*P*＝0.57）[15]。DAWN研究证实对于发病6～24 h但核心梗死与缺血半暗带之间存在错配的患者，取栓治疗相比药物治疗仍可显著改善患者的临床预后[27]，DEFUSE 3团队通过RCT研究发现，发病6～16 h的患者取栓治疗效果同样优于药物治疗[28]。澳大利亚一项针对发病时间或末次正常时间超过6 h或发病时间不明确患者的RCT研究结果提示，此类患者在机械取栓治疗后预后良好率可达62%，出血转化率为7%，且基线NIHSS评分＜16分、基线Alberta卒中计划早期计算机断层扫描评分（Alberta Stroke Program early computed tomography score，ASPECTS）≥8分、术后24 h NIHSS评分＜10分均与良好预后相关[19]。德国的一项注册研究统计了1 917例机械取栓治疗的患者资料，发现11%的患者在发病6～24 h取栓，符合和不符合DAWN和/或DEFUSE 3研究取栓标准的患者预后良好率分别为20%和27%[22]。一项纳入235例患者的单中心研究结果提示机械取栓时间窗并不是影响患者临床预后的明确因素[3]；另一项纳入542例患者的研究中发病超过12 h取栓的患者占4.6%，这些患者取栓治疗后仍可临床获益。以上结果表明经过严格的病例筛选和CTP评估后，超时间窗AIS-LVO的机械取栓仍可能是安全、有效的。

目前关于超时间窗机械取栓的研究多局限于队列研究和回顾性研究，仍缺乏高级别临床证据。目前一项旨在探索AIS-LVO患者超时间窗（发病6～24 h）机械取栓能否获益的多中心、前瞻性RCT临床研究（MR CLEAN-LATE）正在开展，该研究结果或许能提供高级别临床证据[29]。另一项正在开展的研究是TENSION，该研究旨在探讨超时间窗且大核心梗死的缺血性脑卒中患者行机械取栓是否获益[30]。

表 1　AIS-LVO 超时间窗机械取栓相关研究

Tab 1　Studies on mechanical thrombectomy of AIS-LVO beyond time window

Study	Study period	Time window	*N*	90 d mRS score 0-2	Mortality	Conclusion
Peultier, et al[7]	2014-2017	6-24 h	388	NA	NA	Late mechanical thrombectomy added to SMC is cost-effective in all subgroups
Sarraj, et al[14]	2016-2017	6-16 h	182	Direct: 44%; transfer: 45%	Direct: 6%; transfer: 19%	In late-window patients selected by penumbral mismatch criteria, both the favorable outcome rate and treatment effect did not decline in transfer patients
Jadhav, et al[15]	2014-2017	6-16 h; 6-24 h	451; 792	NA	NA	An increase in thrombectomy utilization with important implications for comprehensive stroke center resource optimization and stroke systems of care
Kim, et al[16]	2012-2018	6-24 h	58	55.1%	NA	Collateral-based triage showed good interrater reliability and comparable efficacy to that of perfusion-based triage in predicting clinical outcome after EVT in patients presenting beyond 6 h
Bhan, et al[4]	2016-2018	0-6 h; 6-24 h	147; 88	0-6 h: 37.4%; 6-24 h: 30.7%	0-6 h: 36.7%; 6-24 h: 43.2%	Penumbral imaging-based selection of patients for thrombectomy is effective regardless of onset time and yields similar functional outcomes in early and late window patients
Maslias, et al[17]	2015-2019	0-6 h; 6-24 h	493; 202	NA	NA	The frequency of procedural complications was similar for early and late EVT patients but very short-term outcome seemed less favorable in late EVT patients with complications
Bala, et al[18]	2016-2017	0-6 h; 6-24 h	171; 54	0-6 h: 37.0%; 6-24 h: 37.4%	0-6 h: 24.1%; 6-24 h: 27.5%	EVT using EmboTrap is safe and effective in AIS-LVO patients in the late treatment window
Alsahli, et al[19]	2016-2017	NA	56	62%	14%	A good functional outcome was achieved in 35 (62%) patients
Almekhlafi, et al[20]	NA	NA	35	51.4%	NA	A good functional outcome (90 d mRS score 0-2) was achieved in 16/35 (46%)
Beaulieu, et al[21]	2016-2017	0-6 h; 6-24 h	204; 44	0-6 h: 42%; 6-24 h: 39%	NA	At 3 months, the proportion of patients achieving functional independence (mRS score 0-2) were comparable in the early and late windows (P=0.76)
Herzberg, et al[22]	2015-2018	6-24 h	208	DAWN/DEFUSE 3 eligible: 19.2%; ineligible: 18.5%	DAWN/DEFUSE 3 eligible: 26.9%; ineligible: 33.3%	Good outcome was not significantly higher in trial-ineligible (27%) than in trial-eligible (20%) patients (P=0.343)
Nogueira, et al[23]	2013-2017	0-6 h; 6-24 h	1 173; 430	0-6 h: 55.9%; 6-24 h: 60.6%	0-6 h: 13.0%; 6-24 h: 9.0%	There was no interaction between the treatment time window (0-6 h vs 6-24 h) and CT selection modality (CTP vs NCCT［±CTA］) in terms of functional disability at 90 d (P=0.45)
Escalard, et al[24]	2012-2016	＞6 h	277	45.2%	UOS: 19.3%; KOS: 18.9%	Thrombectomy of UOS with anterior circulation occlusion and DWI-FLAIR mismatch appears to be as safe and efficient as thrombectomy of KOS within 6 h from onset
Desai, et al[25]	2014-2017	6-24 h	142	DAWN eligible: 54%; DEFUSE 3 eligible: 38%; ineligible: 30%	DAWN eligible: 15%; DEFUSE 3 eligible: 13%; ineligible: 24%	A larger population of patients who can potentially benefit from EVT in the expanded time window if more permissive criteria are applied
Nannoni, et al[26]	2003-2017	5-23 h	221	DAWN/DEFUSE 3 eligible: 67%; all: 58%	NA	Late EVT could be offered to a larger population of patients if more liberal criteria are applied

AIS-LVO: Acute ischemic stroke with large vessel occlusion; mRS: Modified Rankin scale; NA: Not reported or not identified; SMC: Standard medical care; EVT: Endovascular treatment; CT: Computed tomography; CTP: Computed tomography perfusion; NCCT: Non-contrast computed tomography; CTA: Computed tomography angiography; UOS: Unknown onset stroke; KOS: Known onset stroke; DWI-FLAIR: Diffusion weighted imaging-fluid attenuated inversion recovery.

3　高级神经影像学是宜行机械取栓超时间窗AIS-LVO患者筛选的重要措施

“越早再通，获益越大”，早期血管再通的概念依然极为重要，时间依然是影响AIS-LVO患者能否从机械取栓治疗获益的决定性因素。然而，随着神经影像学技术的发展和评估体系的完善，可行机械取栓治疗AIS-LVO患者的筛选不应局限于时间窗，而应强化组织窗的概念和拓展取栓时间窗，并充分考虑影像学评估后血管再通治疗的获益及风险。

高级神经影像学评估工具包括RAPID、iSchemaView、MIStar等，这些工具可完成自动化评估，做出独立于医师的判断结果，有助于超时间窗患者的筛选[31]。一项RCT研究对比结果提示，与传统评估工具如CT、MRI等评估后进行机械取栓治疗的患者相比，经高级神经影像学评估筛选的患者机械取栓治疗后血管成功再通率、临床预后均更佳[31]。事实上，目前尚没有可以准确界定核心梗死区或预测临床预后的工具。核心梗死的定义是细胞病理性坏死，包括评估时已经坏死和血管再通前呈进行性坏死的脑组织，而目前的CTP或MRI弥散加权成像（diffusion weighted imaging，DWI）都只是通过脑组织血液灌注程度和神经毒性水肿程度等判断病灶区域的大小。CTP评估中将脑血流量（cerebral blood flow，CBF）＜30%的脑组织区域定义为核心梗死区，但CBF＜5 mL/（100 mg•min）的脑组织在及时血管再通后仍能恢复正常，因此CBF＜30%不等同于核心梗死[32]。寻求一种更为精准的影像学评估工具用于真实坏死脑组织体积和坏死进展速度等的测量，是高级神经影像学评估的发展方向。对于NIHSS评分＞6分、CT检查提示无颅内出血但伴有凝视或反复发作单侧肢体无力的AIS-LVO患者，若在尚未配置高级神经影像学检查设备的医院就诊，医院应将此类患者及时按照流程转送至上级医院或具有相关救治条件的医院，以提高机械取栓成功率及潜在获益率。

组织窗的临床价值高于时间窗。对于超时间窗机械取栓的AIS-LVO患者，末次正常时间不是临床预后良好的独立危险因素，侧支代偿能力和缺血半暗带大小才是预测因素[33]。Vagal等[33]对78例DEFUSE 2研究中的患者进行队列研究，结果显示对于MRI评估存在灌注－弥散错配的患者，再灌注是功能预后良好的独立预测因素（*OR*＝3.7），而发病至治疗时间与功能预后无关（*P*＝0.2）。一项纳入1 246例行机械取栓治疗的AIS-LVO患者的研究结果显示，277例患者的发病至机械取栓时间超过6 h，通过DWI液体抑制反转恢复序列错配评估发现超时间窗取栓患者的临床预后良好率为45.2%，未超时间窗取栓患者的临床预后良好率为53.9%，差异无统计学意义（*P*＞0.05），这一结果证明超时间窗患者仍有可能从机械取栓治疗获益[24]。为进一步研究超时间窗机械取栓的影像学评估，一项RCT研究（SELECT2研究）正在开展，该研究将CT平扫、CTP或MRI评估为大核心梗死且发病24 h内的患者随机分为机械取栓组与药物治疗组，评估经严格影像学筛选后超时间窗机械取栓的有效性[34]。

4　超晚期（发病24 h后）AIS-LVO患者机械取栓的可行性

事实上，发病时间或末次正常时间超过24 h的患者不在少数。一项回顾性病例系列报道了21例超过24 h行机械取栓治疗的AIS-LVO患者，其中9例获得90 d良好预后[35]。一项回顾性研究纳入了429例接受机械取栓治疗的AIS-LVO患者，有5例患者超过24 h取栓，其中4例获得90 d良好预后[36]。考虑临床医师针对发病超过24 h患者更倾向遵循指南推荐的保守治疗，未接受机械取栓治疗的患者比例或许更高，因此可能有更多有潜在获益的患者丧失了取栓机会。既往发表的相关病例系列中最长的取栓时间为发病后29 d[37]，一项病例报告报道了1例发病90 h的大脑中动脉M1段闭塞超晚期机械取栓的患者，该患者获得了良好的临床结局[38]。

超时间窗机械取栓的AIS-LVO患者实现临床获益主要依赖于以下几个方面：（1）病程进展缓慢，源于有良好的侧支代偿及神经元自我保护能力等；（2）较显著的缺血半暗带；（3）密切的神经重症监护条件。发病超过24 h的AIS-LVO患者可能具备以下1个或多个特点才能从机械取栓治疗获益：（1）临床症状较轻，且多以非致残性或轻中度致残性体征为主，如头晕、视物模糊、肢体乏力、偏身感觉障碍等；（2）进行性脑卒中；（3）CTP等检查提示侧支循环及代偿能力较好；（4）核心梗死体积小；（5）粥样硬化性病因占主导地位；（6）影像学表现存在次全闭塞征象且侧支代偿良

好。因此，如何提高神经影像学评估能力、筛选并提高超时间窗 AIS-LVO 患者的机械取栓比例及临床预后仍然是临床的重要课题。

5 小 结

经过严格筛选的超时间窗 AIS-LVO 患者接受机械取栓可能是安全且有效的。目前关于超时间窗机械取栓术对临床预后影响的临床证据不足，亟须在全球化范围内开展多中心、前瞻性 RCT 研究，为规范的超时间窗机械取栓的临床方案制订提供指导。

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