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• 专题报道 •

## 急性大血管闭塞性缺血性脑卒中病因学诊断研究进展

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**[摘要]** 机械取栓已成为急性大血管闭塞(LVO)性缺血性脑卒中的标准治疗手段, 而病因学诊断正日益成为决定治疗策略选择、术后抗栓方案与长期二级预防的关键环节。在急诊场景下, 传统Org 10172急性脑卒中治疗试验分型常面临多机制叠加、检查流程不完整与证据强度不一致等限制, 难以满足快速、可重复的临床需求。2025年缺血性脑卒中表型系统(ISPS25)强调以标准化诊断清单对病因证据进行分层评估, 并将隐匿性心房颤动、肿瘤相关高凝状态、动脉夹层等易被低估的致病机制纳入统一框架, 为急性LVO的病因学诊断与未来临床试验分层提供了更贴近真实世界的实践路径。本文围绕LVO主要病因类型, 系统梳理临床-影像学线索、术中数字减影血管造影表现、人工智能/机器学习多模态推断模型以及血液与血栓相关生物标志物在病因鉴别中的证据要点, 并探讨它们对取栓方式选择、救援性球囊扩张/支架植入策略及术后抗栓方案制定的影响。未来研究应在ISPS25等标准化框架下, 整合CT/CT血管成像/CT灌注成像定量特征、临床变量、实验室指标与术中关键参数, 构建具备快速推理、可解释输出与多中心可迁移的智能病因诊断模型, 并通过前瞻性多中心研究验证其在策略匹配、降低再闭塞/并发症风险、提高二级预防规范水平等方面的临床价值。

**[关键词]** 急性缺血性脑卒中; 大血管闭塞; 病因学诊断; 机械取栓; 颅内动脉粥样硬化性疾病; 心源性栓塞

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### Etiological diagnosis of acute large vessel occlusion ischemic stroke: research progress

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**[Abstract]** Mechanical thrombectomy has become the standard treatment for acute ischemic stroke caused by large vessel occlusion (LVO). Etiological diagnosis is increasingly a critical determinant for endovascular strategy selection, postoperative antithrombotic regimens, and long-term secondary prevention. The conventional Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification often faces limitations in emergency settings, including overlapping mechanisms, incomplete diagnostic workflows, and inconsistent levels of evidence quality, making it difficult to meet the rapid and reproducible clinical requirements. The ischemic stroke phenotyping system 2025 (ISPS25) emphasizes hierarchical evaluation of etiological evidence using a standardized diagnostic checklist, incorporating underrecognized pathogenic mechanisms (such as occult atrial fibrillation, cancer-related hypercoagulability, and arterial dissection) into a unified framework, thereby providing a more real-world paradigm for etiological assessment of acute LVO and future trial stratification. This review focuses on the major etiological subtypes of LVO and systematically summarizes key evidence for etiological differentiation from multiple dimensions, including clinical-imaging indicators, intraoperative digital subtraction angiography characteristics, artificial intelligence and machine learning-based multimodal inference, and blood- and thrombus-related biomarkers. It further discusses how these factors influence thrombectomy technique selection, rescue balloon angioplasty or stenting strategies, and postoperative antithrombotic protocols. Future research should integrate quantitative features from computed tomography (CT)/CT angiography/CT perfusion, clinical variables, laboratory indicators, and intraoperative parameters under standardized frameworks such as ISPS25, so as to construct an intelligent etiological diagnostic model with rapid inference capability, interpretable outputs and multicenter generalizability, and validate its clinical value in treatment-strategy matching,

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reducing reocclusion and complication risks, and optimizing secondary prevention strategies via prospective multicenter studies.

[ **Key words** ] acute ischemic stroke; large vessel occlusion; etiological diagnosis; mechanical thrombectomy; intracranial atherosclerotic disease; cardioembolism

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自2015年多项随机对照试验(如MR CLEAN、ESCAPE、EXTEND-IA、SWIFT PRIME、REVASCAT<sup>[1-5]</sup>)确立机械取栓为急性大血管闭塞(large vessel occlusion, LVO)性缺血性脑卒中的一线治疗手段以来,围绕“快速再灌注”的技术体系已逐渐成熟,而病因学诊断正成为影响术中策略、术后抗栓方案及长期二级预防的关键环节。现阶段临床病因学诊断仍主要采用Org 10172急性脑卒中治疗试验(Trial of Org 10172 in Acute Stroke Treatment, TOAST)分型<sup>[6]</sup>,然而在急诊情境下,LVO患者常存在多机制叠加(如颅内动脉粥样硬化狭窄合并栓塞)、检查流程不完整及病因证据强度不一致等问题,其操作一致性与推广价值有限。2025年缺血性脑卒中表型系统(ischemic stroke phenotyping system 2025, ISPS25)强调以标准化诊断清单对病因证据进行分层(明确/疑似/可能),并将隐匿性心房颤动、肿瘤相关高凝状态、动脉夹层等易被低估的病因机制纳入通用性更强的统一框架,为急性LVO的病因学诊断与未来试验分层提供了更贴近真实世界的实践路径<sup>[7]</sup>。本文综述了急性LVO的主要病因类型、鉴别证据及其对血管内治疗策略的影响,并结合人工智能与新兴生物标志物研究进展探讨未来多模态整合的病因学评估发展方向。

## 1 LVO病因分型及其对治疗的影响

按照TOAST分型标准,LVO病因可分为大动脉粥样硬化[large artery atherosclerosis, LAA;包括颅内动脉粥样硬化性疾病(intracranial atherosclerotic disease, ICAD)]、心源性栓塞(cardioembolism, CE)、不明原因和其他明确病因四大类<sup>[6]</sup>。

ICAD相关LVO在亚洲及非洲人群中高发,占LVO病因的30%~50%<sup>[8]</sup>。其病理基础为不稳定性斑块破裂触发原位血栓形成(*in situ* thrombosis);部分病例中,血栓脱落后可沿血管

迁移导致远端动脉-动脉栓塞,进一步扩大闭塞范围,增加再灌注治疗难度<sup>[9-11]</sup>。血栓组织学分析显示,LAA相关血栓主要是红细胞含量高、纤维蛋白和血小板含量较低的“红血栓”,且中性粒细胞诱捕网形成相对较少<sup>[12]</sup>。

CE占LVO病因的19%~25%,在欧美人群中占比更高,常源于心房颤动、心肌病或瓣膜性心脏病等中高危及心脏病变<sup>[13-14]</sup>。CE相关血栓以血小板和纤维蛋白含量高、红细胞含量低的“白血栓”为主,且伴有丰富的中性粒细胞诱捕网形成和免疫细胞浸润<sup>[12]</sup>。此外,动脉夹层、烟雾病、血管炎等非粥样硬化性疾病以及血液高凝状态等也可能导致LVO,此类病因占LVO病因的5%~15%<sup>[8,15]</sup>。

即使经过长程心电监测等系统病因学检查,仍有15%~30%的LVO患者无法明确病因,被归为不明原因型卒中<sup>[16-17]</sup>。目前普遍认为不明原因型卒中可能是一个高度异质性的群体,既可能由隐匿性阵发性心房颤动、卵圆孔未闭等隐匿性心脏疾病引发,也可能是动脉粥样硬化易损斑块表面微血栓脱落所致<sup>[18-19]</sup>。

不同病因LVO的取栓方式和术后管理方案往往差异显著,其中与临床意义最为突出的是ICAD相关闭塞与CE型闭塞的鉴别。对于ICAD,术中需要重点考虑对原位狭窄部位进行扩张<sup>[11,20-21]</sup>。CE及不明原因型卒中往往源于栓子栓塞,闭塞部位血管壁相对平滑,通常不需要原位扩张,术中多采用支架取栓或直接抽吸方式清除栓子<sup>[22-23]</sup>。病因学诊断对LVO性缺血性脑卒中患者的术后管理也有明显的指导作用,ICAD通常需要强化双联抗血小板方案(如阿司匹林+氯吡格雷)联合他汀类药物,而CE则优先采用抗凝治疗(如直接口服抗凝药物)<sup>[24-26]</sup>。

## 2 LVO病因学诊断的常用方法

2.1 基于临床-影像信息的病因鉴别 CE和ICAD是颅内LVO最常见的两大病因,两者在临床表现、影像学特征及危险因素方面均存在显著差异。

CE通常呈急性起病,患者常有心脏病史(如心房颤动、瓣膜性心脏病、近期心肌梗死等)<sup>[27]</sup>;而ICAD患者常伴随系统性血管危险因素,如吸烟、高血压、糖尿病和高脂血症等<sup>[28]</sup>。

CE和ICAD的影像学表现也存在显著差异。在闭塞部位方面,ICAD往往表现为主干型闭塞(truncal-type occlusion),而CE常表现为分叉型闭塞(branching-type occlusion)。在血栓特征方面,磁共振T2\*加权梯度回波成像中的磁敏感血管征(susceptibility vessel sign, SVS)可反映血栓中含铁血红蛋白的分布。研究表明,SVS在CE患者中出现频率极高,而在动脉粥样硬化性狭窄或慢性闭塞的病例中很少见,是鉴别两者的强有力影像学指标<sup>[29-30]</sup>。血栓增强征也与CE密切相关( $OR=22.2, 95\%CI 9.4\sim 53.8, P<0.001$ ),可用于病因鉴别<sup>[31]</sup>。在缺血范围及灌注特征方面,ICAD相关闭塞患者梗死体积往往较小、美国国立卫生研究院卒中量表评分相对较低<sup>[32-33]</sup>,且影像学上可观察到合并其他血管狭窄。Yoshimoto等<sup>[34]</sup>基于CT灌

注成像(CT perfusion, CTP)参数发现,当低灌注强度比(达峰时间 $>10s$ 与 $>6s$ 脑组织体积的比值) $\leq 0.22$ 时,提示LVO病因为ICAD。

近年来,研究者已对基于临床信息和影像学特征的病因预测模型进行了初步探索。Liao等<sup>[35]</sup>构建的ABC2D评分(整合心房颤动史、高血压病史、美国国立卫生研究院卒中量表评分 $<7$ 分、CT高密度征、糖尿病史)诊断ICAD的AUC值达0.880(95%CI 0.846~0.914)。Zhang等<sup>[32]</sup>提出的AHOC评分(心房颤动病史、CT高密度征、合并其他血管狭窄、侧支代偿情况)在验证组中AUC值达0.933(95%CI 0.888~0.978)。然而,目前影像学特征仍以人类主观识别为主,未来需引入更多定量影像组学特征以提高诊断的客观性与可重复性。为便于在急诊情境下整合病因分类、影像学线索及治疗策略,本文将ICAD相关闭塞与栓塞性闭塞(以CE为代表)的主要鉴别要点及其术中与术后管理策略进行了结构化归纳,见表1。

表1 急性LVO中ICAD相关闭塞和栓塞性闭塞的鉴别证据及其治疗策略

Tab 1 Integrated evidence for differentiating ICAD-related and embolic occlusion in acute LVO and their therapeutic strategies

Dimension	ICAD-related LVO ( <i>in situ</i> stenosis/thrombosis)	Embolic LVO (commonly CE)
Population and risk factor	Hypertension, diabetes, smoking, and dyslipidemia are more common; higher proportion in Asian populations	History of heart diseases such as atrial fibrillation, valvular heart disease, cardiomyopathy, and recent myocardial infarction are more common
Occlusion morphology	More prone to truncal-type occlusion, residual stenosis is often visible	More prone to branching-type occlusion, vessel wall is relatively smooth
Thrombus imaging clue	Negative SVS is relatively more common; collateral circulation may be better; and HIR is relatively lower	Positive SVS and thrombus enhancement sign are more common; embolus burden is often larger
Intraoperative manifestation	Prone to re-occlusion or fixed stenosis after thrombectomy; microcatheter "first-pass effect" can be observed	The first recanalization rate is relatively higher; residual stenosis is rare
Intraoperative strategy preference	Rescue balloon angioplasty or stenting may be required	Stent retriever or direct aspiration alone are mostly sufficient
Postoperative antithrombotic strategy	Tend towards intensive dual antiplatelet therapy+statins	Prioritize anticoagulant therapy if indications are met
Main challenge	Difficult to differentiate when <i>in situ</i> stenosis and embolism coexist	Etiology remains uncertain when occult atrial fibrillation or cardioembolic evidence are insufficient

LVO: Large vessel occlusion; ICAD: Intracranial atherosclerotic disease; CE: Cardioembolism; SVS: Susceptibility vessel sign; HIR: Hypoperfusion intensity ratio.

2.2 基于人工智能与机器学习技术的多模态病因诊断 目前LVO病因鉴别面临的核心矛盾是:急诊需要“快”,而病因证据往往来自临床危险因素、CT/CT血管成像/CT灌注成像、血栓特征、生

物标志物与术中数字减影血管造影征象等多源、异质、强交互的信息,难以在短时间内完成整合与精准判断。人工智能与机器学习为此提供了两条切实可行的路线:其一,基于常规影像的定量表

征,如CT/CT血管成像上的血栓密度、长度、增强模式及影像组学特征,构建监督学习模型,实现对栓塞性机制(如CE)和动脉粥样硬化相关机制(如ICAD原位血栓/狭窄)的概率输出。其二,将影像定量特征与临床变量、实验室指标进行多模态融合建模,在保证推理速度的同时提升泛化性能。已有研究证实,基于CT影像组学区分CE与动脉粥样硬化性血栓来源的技术路径具有可行性,但早期研究多存在样本量较小、外部验证不足等局限<sup>[36-37]</sup>。

实现上述路径临床转化的关键在于:(1)建立与真实急诊流程匹配的输入(优先CT/CT血管成像/CT灌注成像+基线实验室指标);(2)开展多中心外部验证与前瞻性队列评估;(3)输出可解释特征的贡献以增强临床信任与可追溯性;(4)与ISPS25等标准化病因诊断框架对齐,形成“证据分层+概率输出”的组合式报告,服务于术中策略(如是否需行救援性球囊扩张/支架植入)与术后抗栓策略选择<sup>[7]</sup>。

**2.3 基于血液生物标志物的病因鉴别** 血液生物标志物具有采集简便、结果客观、可通过急诊快速检测/床旁检测嵌入急诊流程等优势,能弥补影像征象对操作者依赖度高、对复杂/后循环卒中病例不够稳健的短板<sup>[38]</sup>。Gao等<sup>[39]</sup>利用年龄、白细胞计数、天冬氨酸转氨酶、非高密度脂蛋白胆固醇等常规实验室参数构建了LVO卒中病因预测模型,区分CE与动脉粥样硬化性闭塞的AUC值为0.80。凝血/纤溶相关指标D-二聚体在CE或血液高凝相关卒中患者中水平往往更高,具有病因方向性提示价值<sup>[40]</sup>。近期一项meta分析纳入10项研究,证实D-二聚体在发病24h内对脑栓塞具有中等诊断性能(汇总灵敏度为0.77、特异度为0.79,AUC值为0.85),为在倾向栓塞表型快速分层中的应用提供了更系统的证据支持<sup>[41]</sup>。由于感染、肿瘤、创伤、年龄等多因素影响,单指标常常难以满足急诊个体化决策需求。相比之下,心房/心室负荷相关肽类如脑钠肽、氨基末端脑钠肽前体(N-terminal pro-brain natriuretic peptide, NT-proBNP)、心房利尿钠肽及心房利尿钠肽中段前体(midregional pro-atrial natriuretic peptide, MR-proANP),更贴近潜在心源性机制的病理生理基础。多中心前瞻性队列研究表明,发病24h内MR-proANP水平

与CE、新诊断心房颤动及心血管不良事件风险相关,可指导临床延长心电监测时间及进一步心源性检查选择<sup>[42]</sup>。近期一项队列分析同样提示,MR-proANP与NT-proBNP能用于识别心房颤动检出概率低的人群,可在不降低心房颤动检出量的情况下减少不必要的延长监测,凸显其在规则化病因分层中的潜在卫生经济学价值<sup>[43]</sup>。此外,多项针对MR-proANP与CE型缺血性脑卒中关联的系统综述与meta分析均证实,MR-proANP具备作为“心源性机制概率”标志物的潜力,但仍需统一检测时点、阈值,并开展与临床/影像联合建模的外部验证<sup>[44-45]</sup>。

值得关注的是,外周血标志物与血栓本身标志物在病因鉴别中可形成互补,有研究者尝试了对取栓血栓中的DNA与D-二聚体含量进行定量检测并用于区分心源性与非心源性血栓(AUC值为0.79)<sup>[46]</sup>。这提示未来或可构建“术前外周血检测+术中血栓组学分析”的分层与反馈闭环方案,但其临床转化仍受检测标准化与时间成本限制。

**2.4 血管内治疗的术中病因鉴别** 血管内治疗术中数字减影血管造影结果可为病因鉴别提供参考。动脉粥样硬化性狭窄患者闭塞血管近端常可观察到锥形狭窄(tapered narrowing),且闭塞多位于大脑中动脉主干等非分叉区域<sup>[8]</sup>,但该征象对病因鉴别的特异性较低。Yi等<sup>[47]</sup>提出了微导管首次通过效应(microcatheter first-pass effect),使用0.014英寸(1英寸=2.54 cm)微导丝引导微导管(通常2.1F)穿过闭塞段到达远端通畅血管后,保持微导丝原位不动,将微导管缓慢撤回至闭塞段的近端进行造影观察,若闭塞段远端出现缓慢、暂时的前向血流,提示ICAD相关闭塞(存在原位血栓或粥样硬化性斑块,微导管通过时暂时撑开狭窄血管使少量血流通过);若远端无血流或仅见少量造影剂滞留,则提示栓塞性闭塞(血栓致密,微导管通过后狭窄血管迅速闭合)。这一方法在小样本人群中准确度达到88.5%<sup>[47]</sup>,但仍有待大样本研究进一步证实。此外,最近有研究提出“改良首次通过效应”,并在小样本注册队列中用于直接指导“先成形、后(或不)取栓”的术中策略,结果提示该方法可缩短穿刺至再通时间并改善临床结局,但仍需更大规模前瞻性研究验证并确认其安全性和适用边界<sup>[48]</sup>。

### 3 总结和展望

急性LVO病因鉴别研究虽已形成“临床-影像-生物标志物-术中观察”的多线索体系,但目前仍受限于样本量、单中心研究偏倚、外部验证不足和急诊时效性限制等诸多瓶颈;同时,人群构成差异(如亚洲人群ICAD占比偏高)与多机制重叠导致单线索模型的误判风险增加。短期内,基于常规影像(CT/CT血管成像/CT灌注成像)与基线临床信息的快速评估仍是最具可及性的方法;中长期应以ISPS25等标准化病因诊断框架为基础,整合临床变量、影像定量特征(包括影像组学、深度学习特征)、血液生物标志物及术中数字减影血管造影信息等多模态信息,构建具备快速推理、可解释输出与多中心可迁移的智能病因诊断模型,同时通过前瞻性、多中心研究验证其能否优化术中策略匹配、降低再闭塞与并发症风险,并进一步提升二级预防的准确性与一致性。

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