·脑卒中研究进展·

急性缺血性卒中机械取栓术后血栓标本组织病理学研究进展

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【摘要】 脑卒中是全球第二大死因，也是我国主要死因，其中缺血性卒中约占70%。血管内机械取栓术业已成为急性缺血性卒中的有效治疗方法，但预后不良发生率仍高达50%。机械取栓术的问世使临床收集血栓标本进行组织病理学研究成为可能，同时亦避免体外研究和动物实验的局限性。本文对血栓组织病理学、血栓影像学、血栓组织病理学与病因分型、血栓组织病理学与血管内治疗等进展进行综述，旨在探究血栓形成的病理生理学机制，为急性缺血性卒中的诊疗提供潜在靶点。

【关键词】 卒中；　脑缺血；　血栓切除术；　病理学；　综述

Histopathological research progress of thrombus retrieved by mechanical thrombectomy from patients with acute ischemic stroke

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【Abstract】 Stroke is the second leading cause of death in the world and the main cause of death in China. Ischemic stroke accounts for 70% of the total number of stroke. Endovascular mechanical thrombectomy has been recognized as an effective treatment for acute ischemic stroke (AIS) recently, however, the percentage of patients who were subject to poor prognosis and had relatively high morbidity and mortality is about 50%. The development of mechanical thrombectomy makes it possible to collect thrombus retrieved from intravascular therapy for more histopathological researches. It allows more complete extraction of human thrombus for histological analysis, while avoiding the limitations of invitro and animal experiments. This article reviews the progress of thrombus histopathology, thrombus imaging, thrombus histopathology and etiology classification, thrombus histopathology and intravascular therapy, in order to explore the pathophysiological mechanism of thrombosis and provide potential targets for the diagnosis and treatment of acute ischemic stroke.

【Key words】 Stroke;　Brain ischemia;　Thrombectomy;　Pathology;　Review

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Conflicts of interest: none declared

脑卒中是全球第二大死因[1]，每年约1370万例发生脑卒中，有580万例死于脑卒中，其中缺血性卒中病例约占全部脑卒中的70%[2]。脑卒中是我国主要死因，根据2017年中国卒中大数据（Ness-China）统计，我国每年约有240万例新发脑卒中病例以及110万例脑卒中相关死亡病例[1]。尽管临床采取强化调脂治疗和负荷剂量抗血小板治疗，但在低密度脂蛋白胆固醇（LDL-C）降低的情况下，仍面临脑血管事件反复发生的风险。血管内机械取栓术是急性缺血性卒中治疗领域的重要进展，可显著改善急性大动脉闭塞致缺血性卒中患者预后，其血管再通率可高达90%以上[3-6]，但仍有约7.2%的患者术后24小时内发生血管再闭塞[7]，且术后3个月预后不良发生率[改良Rankin量表（mRS）评分＞2]高达

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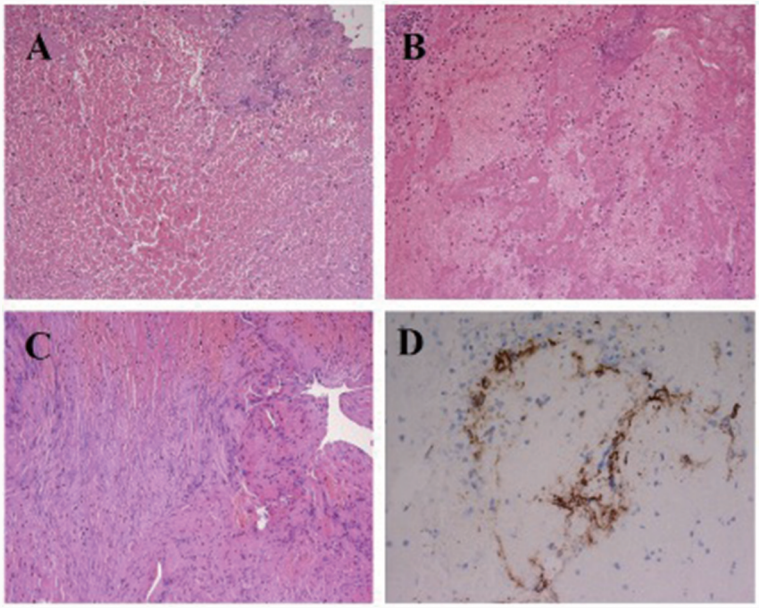

图1　急性缺血性卒中血栓标本的4种病理学类型(光学显微镜观察)[13]　低倍放大　1a以红细胞为主的血栓　HE染色　1b　红细胞与纤维蛋白比例相当的血栓　HE染色　1c以纤维蛋白为主的血栓　HE染色　1d　组织化纤维蛋白血栓　CD34免疫组化染色

Figure 1　Stained histology sections of thrombi retrieved by thrombectomy from AIS patients demonstrating four pathology categories[13]. Low power magnified　RBC dominance in a HE stained section (Panel 1a). RBC equal to fibrin in a HE stained section (Panel 1b). Fibrin dominance in a HE stained section (Panel 1c). Organised fibrin thrombosis in a CD34 immunohistochemical stained section (Panel 1d).

46.7%～53.3%[8-9]，可能是由于急性缺血性卒中的发病机制除血栓形成外，还有其他影响因素的参与。血管内机械取栓术的问世可以对血栓进行较完整的提取和组织学分析，同时避免体外研究和动物实验的局限性。血栓病理学研究有助于探究血栓的发生机制，寻找急性缺血性卒中潜在的更有效治疗靶点，采取更精准的治疗措施[10]。本文拟对急性缺血性卒中血栓组织病理学、血栓影像学，以及血栓组织病理学与病因分型、血栓组织病理学与血管内治疗等进展进行综述，并对未来研究方向和潜在治疗靶点进行展望。

一、组织病理学研究

1.组织学形态和免疫表型　血栓的主要成分为纤维蛋白、血小板、白细胞和红细胞。Marder等[11]于2006年首次报告其针对急性缺血性卒中血栓组织学形态的系统分析结果，由HE染色可见，经Merci取栓器回收的25例前循环缺血性卒中患者的血栓标本均具有独特的组织学外观即异质性，但绝大多数血栓存在相似的结构特征，包括纤维蛋白-血小板沉积、呈线性分布的有核细胞(单核细胞和中性粒细胞)，以及局灶性富含红细胞的区域，且未发现明显的胆固醇晶体。这种纤维蛋白-血小板模式的血栓结构，为缺血性卒中预防策略中抗血小板和抗凝治疗提供了理论依据，也为大规模临床试验提供了基础佐证。Simons等[12]对40例急性缺血性卒中患者的血栓标本进行HE染色和CD34免疫组化染色，根据不同血栓成分所占比例分为4种类型，即伴少量纤维蛋白浸润以红细胞为主的血栓、红细胞与纤维蛋白比例相当的血栓、以纤维蛋白为主的血栓、CD34免疫组化染色阳性提示内皮细胞增生的组织化纤维蛋白血栓。通过血栓成分研究有助于确定血栓的形成时间(图1)[13]。根据血栓形成时间，动脉血栓可以分为新鲜血栓(<1天)、溶解性血栓(1～5天)和组织化血栓(>5天)[14]，新鲜血栓表现为富含红细胞区域散在分布纤维蛋白和完整的白细胞；陈旧性血栓包括溶解性血栓(中性粒细胞溶解、坏死和核碎裂)和组织化血栓(平滑肌细胞向血栓内部生长，伴或不伴结缔组织沉积)[15]。由于血栓形成遵循明确的时间顺序，血小板先在血管内皮损伤部位粘附并募集更多的血小板，在血小板-纤维蛋白结合物形成之前，白细胞即开始在血小板边缘聚集，鉴于血小板的这一特点，有学者认为可以白细胞含量作为血栓组织化程度的标志物，并以此代表血栓形成时间[16]。既往10余年间，血管性血友病因子(vWF)作为血栓的重要组成部分受到广泛关注，该因子为多聚体血浆糖蛋白，通过在血管内皮损伤部位募集血小板以介导血栓形成并参与血栓稳定机制[17-18]。已知缺血性卒中血栓组织中所含的大量vWF不易被rt-PA溶解，但可被整合素样金属蛋白酶与凝血酶13型(ADAMTS13)溶解，该效应具有剂量依赖性，并且其溶栓效果业已经动物模型验证[19]，因此，vWF有望成为改善缺血性卒中溶栓效

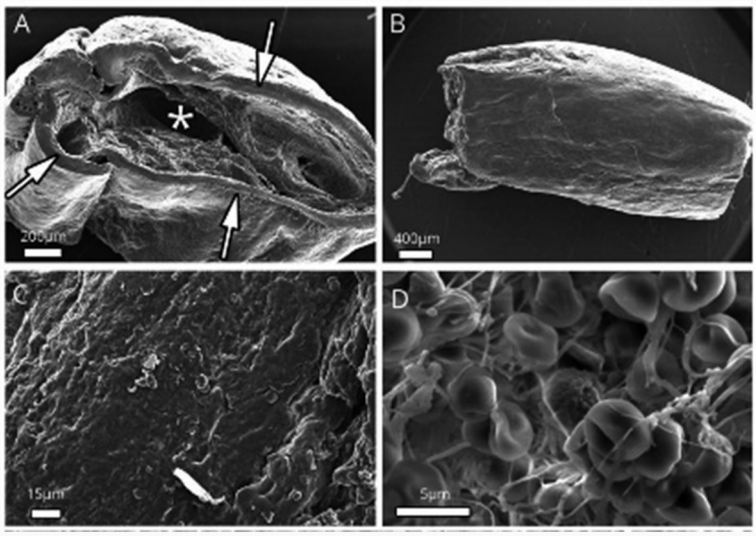

图2　急性缺血性卒中血栓标本的超微结构特征(扫描电子显微镜观察)[24]　2a　血栓横截面可见致密而连续的外壳(箭头所示)包裹着松散的血栓核心(星号所示)　低倍放大　2b　可见血栓外壳的均质性和连续性　低倍放大　2c　血栓外壳成分联系紧密,难以区分单个细胞或纤维　高倍放大　2d　血栓核心内细胞轮廓清晰,易于辨认　高倍放大

Figure 2　Scanning electron microscopy imaging characteristics of thrombi retrieved by thrombectomy from AIS patients [24]. Transversal cross-section of a thrombus showed the presence of a dense compacted peripheral layer forming a continuous shell (arrows indicate) encapsulating the thrombus core (asterisk indicates, Panel 2a). Low magnification view of the surface of another part of the same thrombus highlights the homogeneous and continuous aspect of the thrombus shell (Panel 2b). Low magnification view of the shell surface, in which individual cells could hardly be detected (Panel 2c). High magnification view of the inner core, in which cells and fibrin fibers were clearly identifiable (Panel 2d).

果的新靶点[20]。

2.超微结构　急性缺血性卒中血栓的超微结构亦具有异质性[21-22]。Nogueira等[23]对18例急性缺血性卒中患者的血栓标本进行扫描电子显微镜观察,发现两种组织结构模式:(1)血栓呈高度成熟状态,所有血栓成分均紧密结合在一起,各成分之间边界模糊,表明该区域已成熟且持续显露于剪切流中。(2)血栓组织中纤维蛋白网及其中的红细胞清晰可见,血栓成分有松散的交联特性,表明血栓仍处于成熟过程中且位于血流淤积和再通的活动区域。不同患者的血栓呈现不同比例的上述模式,目前尚不清楚此模式的形成原因。Di Meglio等[24]对30例急性缺血性卒中患者的血栓标本进行扫描电子显微镜观察,发现大多数血栓存在固有的组织结构特征——壳核。壳核的外壳是由纤维蛋白、vWF和聚集的血小板等构成的致密层,细胞成分被紧密压缩在一起,边界不清,外壳内包裹着一个松散的富含红细胞的核心,核心内细胞轮廓清晰,易于辨认红细胞、纤维蛋白和聚集的血小板(图2)。基于人类血液标本的血栓形成体外研究证实,血小板是形成这种血栓外壳的关键成分。相比血栓核心,外壳的抗溶解能力更强,因此壳核的存在限制了血栓对溶栓治疗的敏感性[24]。

二、影像学表现

临床采用无创性影像学技术如CT和MRI观察急性缺血性卒中血栓征象已有20余年的历史。目前对血栓的影像学诊断已成为急性缺血性卒中诊断与治疗的重要部分,可明确血栓部位、大小和成像特性等信息[25-27]。例如,CTA不仅可用于评估血栓负荷,明确血栓部位并测量血栓大小,还可以帮助术者选择取栓工具,特别是对支架取栓工具类型和长度的选择[28-29]。

理论上由于血栓大小及其成分不同,其物理性质必然具有一定的差异。于疾病早期通过影像学检查识别不同血栓成分,一直是影像诊断学的发展目标[30-33]。动物实验支持血栓成像与组织病理学的相关性:Fujimoto等[34]将富含红细胞或富含纤维蛋白这两种不同类型血栓分别注入猪颈总动脉,然后行MRI检查,发现富含红细胞的血栓在FLAIR成像上呈高信号、T_2*WI呈等信号,而富含纤维蛋白的血栓在FLAIR成像上呈等信号、T_2*WI呈低信号。Liebeskind等[30]的临床研究显示,急性缺血性卒中早期血栓影像学表现与组织病理学之间存在一定的关联性,其通过对50例血栓标本和影像学资料的回顾分析,发现CT的大脑中动脉高密度征(HMCAS)和MRI梯度回波序列(GRE)的晕状伪影(blooming artifact)主要见于以红细胞为主的血栓和混合血栓,而且表现为大脑中动脉高密度征和晕状伪影的血栓红细胞比例更高。由此可见,红细胞含量决定是否出现大脑中动脉高密度征和晕状伪影,而不存在大脑中动脉高密度征或晕状伪影的血栓可能是以纤维蛋白为主的血栓,后者是纤溶治疗的主要目标。2020年,Janot等[35]通过体外研究提出一种结合磁敏感加权成像(SWI)、T_2WI和FLAIR成像定量测定血栓中红细胞含量的方法,但存在一定局限性。

血栓CT值也有助于判断血栓成分。CT值可表示血栓衰减系数，单位为HU[35-36]，血红蛋白含量是血栓衰减的决定因素之一，血小板和动脉粥样硬化碎片可明显减少血栓衰减[37]。Niesten等[15]对22例急性缺血性卒中患者机械取栓术后所获得的血栓成分进行分析，发现CT值与红细胞含量呈正相关（$r=0.401$，$P=0.049$），证实了CT作为急性缺血性卒中治疗的影像学标志物的有效性。但值得注意的是，该项试验中有20例患者分别于静脉或动脉注射rt-PA后再行机械取栓术，与血小板相比，红细胞对rt-PA的敏感性更高，因此这种线性相关关系实际上更强。Songsaeng等[38]的研究采用CT、CTA和增强CT（CE-CT）评估不同类型血栓，发现红色血栓与白色血栓（CT：$P=0.001$，CTA：$P=0.014$，CE-CT：$P=0.001$），红色血栓与混合血栓（CT：$P=0.043$，CTA：$P=0.002$）的HU值差异均有统计学意义。由此可见，早期识别CT和MRI的影像学特征有助于鉴别和预测血栓成分。

三、组织病理学与病因分型和临床预后

1.病因分型　急性缺血性卒中的病因分型对指导脑卒中预防、减少复发具有决定意义。TOAST（The Trial of Org 10172 in Acute Stroke Treatment）分型是目前国内外应用最广泛的病因分型依据[1]。血栓的组织病理学结果有助于判断缺血性卒中的病因[39]。近年开展的一项针对不同病因的急性缺血性卒中机械取栓标本的组织病理学研究共纳入187例患者，包括心源性卒中77例、非心源性卒中46例[大动脉粥样硬化（LAA）型和其他明确病因（SOE）型]和隐源性脑卒中64例，分别行HE染色、Elastica van Gieson染色、普鲁士蓝染色和免疫组化染色，结果显示，与非心源性卒中相比，心源性卒中患者血栓纤维蛋白/血小板比值（$P=0.027$）和白细胞含量（$P=0.026$）更高，而红细胞含量更低（$P=0.005$）[40]。Simons等[12]和Boeckh-Behrens等[41]的研究结论被视为其佐证。晚近研究显示，红细胞在冠状动脉粥样硬化斑块由稳定向不稳定的转变过程中发挥至关重要的作用[42]，这可以解释LAA型患者血栓红细胞含量更高。此外，与直接在斑块破裂部位形成血栓相比，心源性卒中血栓形成所需时间更长、组织化程度更高，白细胞有更多的时间和机会侵入血栓内部，故心源性卒中血栓白细胞比例更高[41]。对血栓成分的分析还有助于探究隐源性脑卒中的发病机制[43]。Sporns等[40]的研究认为，隐源性脑卒中与心源性卒中的组织病理学具有相似性。Boeckh-Behrens等[44]发现，隐源性脑卒中和心源性卒中血栓的纤维蛋白/血小板比值均高于、红细胞比例均低于非心源性卒中，而二者之间纤维蛋白/血小板比值和红细胞比例差异无统计学意义。上述研究结论均支持大多数隐源性脑卒中可能存在心源性栓塞（CE）型的假说，即隐源性脑卒中多起源于心脏[44-45]。同时也提出了一个重要的假设，即抗凝治疗可能对隐源性脑卒中有益[46]。然而，亦有学者得出的结论与上述研究相矛盾，Kim等[47]发现，心源性卒中血栓红细胞比例更高、纤维蛋白比例更低，究其原因，可能与样本量较小（37例）、所纳入病例中多数（62.1%）于机械取栓前即已接受rt-PA静脉溶栓而影响血栓成分有关。

2.临床预后　血栓成分是决定血管再通成功的关键[48-49]。一项系统评价显示，机械取栓前头部CT存在大脑中动脉高密度征的急性缺血性卒中患者术后更易获得良好的血管再通（$P=0.004$）[50]。大脑中动脉高密度征常提示血栓红细胞比例较高[11,50]，因此，以红细胞为主的血栓更易通过血栓切除术清除。Hashimoto等[51]研究显示，经血管内治疗获得成功再灌注的急性缺血性卒中患者，其血栓内粥样硬化斑块较少、红细胞比例较高，且斑块（$OR=0.062$，95%CI：0.002～0.864；$P=0.038$）和红细胞比例＞64%（$OR=4.352$，95%CI：1.185～19.363；$P=0.026$），这些均为血管成功再通的影响因素。以红细胞为主的血栓黏度和变形性增加、弹性和刚性降低，使其不易破碎，而易切除；而斑块易破裂为小的碎片，可能降低血栓切除术的效果。此外，对于动脉粥样硬化性狭窄的患者，血栓切除术更易对管壁造成不可逆性损伤，也是其再灌注失败的原因[52]。随着病程的延长，血栓粘附于管壁的稳定性和强度增加，同时亦使手术难度增加，因此，血栓的形成时间对机械取栓术的成功亦十分重要[53]。Almekhlafi等[54]研究认为，内皮化是血栓呈亚急性的标记，由于溶栓药物不易透过血管内皮，故血管内皮的覆盖程度可能影响静脉溶栓效果。Boeckh-Behrens等[41]发现，机械取栓术后部分血管再通[脑梗死溶栓血流分级（TICI）为2b级]患者血栓白细胞比例明显高于完全血管再通（TICI分级为3级）患者（$P=0.030$），且血栓白细胞比例与出院时神经功能缺损程度[美国国立卫生研究院卒中量表（NIHSS）评分]呈正相关（$r=0.394$，$P=0.023$）。纤维蛋白含量也可以影响

rt-PA溶栓效果和血管内机械取栓术后血管再通情况[55]。对急性缺血性卒中兔模型的rt-PA溶栓疗效观察发现，与富含红细胞的血栓相比，以纤维蛋白为主的血栓rt-PA溶栓效果较差[56]。对急性缺血性卒中猪模型机械取栓术的疗效观察显示，以纤维蛋白为主的血栓比富含红细胞血栓的血管再通率更低、血管再通时间更长[57]。

四、炎症介质在急性缺血性卒中血栓发生发展中的作用

炎症反应与动脉粥样硬化性血栓形成和缺血性脑血管事件密切相关[58-59]。研究显示，大动脉粥样硬化发生发展的不同阶段（脂质条纹期、纤维性斑块期、粥样硬化斑块期、不稳定斑块期、斑块破裂期和血栓形成期），其病变局部始终伴随着炎症反应[60-61]；血栓标本中同样也存在炎性细胞和炎性因子[62]。其中，白细胞作为炎性细胞始终存在于血栓组织中[31,41]。Laridan等[63]对急性缺血性卒中血栓标本的HE染色发现，血栓内含有大量白细胞且均为有核细胞；进一步行中性粒细胞标志物CD66b和中性粒细胞弹性蛋白酶（NE）免疫组化染色，结果证实大多数白细胞为嗜中性粒细胞；中性粒细胞胞外杀菌网络（NETs）标志物瓜氨酸化组蛋白H3（H3Cit）染色呈阳性；最终经CD66b和DNA染料4’，6-二脒基-2-苯基吲哚（DAPI）免疫荧光染色证实胞外杀菌网络是急性缺血性卒中血栓的常见成分。与其他类型缺血性卒中的血栓相比，CE型血栓胞外杀菌网络含量增加；与新鲜血栓相比，陈旧性血栓胞外杀菌网络含量增加。值得注意的是，新鲜血栓的体外溶解实验显示，针对胞外杀菌网络靶向添加脱氧核糖核酸酶Ⅰ（DNase 1）联合t-PA溶栓效果较单纯t-PA溶栓具有更强的血栓溶解作用[63]。

采用免疫组化检测对血栓白细胞亚型进行分析也有助于明确炎性细胞在血栓形成中的作用。LAA型血栓$CD3^+$T细胞数目明显高于CE型[64]。由于不稳定型斑块破裂的最后一步是活化的T淋巴细胞释放弹性蛋白酶和基质金属蛋白酶（MMPs），因此LAA型血栓T淋巴细胞数目更高是符合逻辑的。

综上所述，通过探究急性缺血性卒中机械取栓术后血栓标本的组织病理学特征，可以反映不同血栓成分相关临床特征，阐明血栓形成的病理生理学机制[65]，以及炎症反应在不同病因分型缺血性卒中血栓形成中的作用，以为急性缺血性卒中的诊疗提供潜在靶点。

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