

# 急性缺血性卒中血管内治疗血栓标本胆固醇结晶分析

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**【摘要】 目的** 比较急性缺血性卒中不同病因分型患者血栓标本胆固醇结晶比例的差异,并探讨含胆固醇结晶的血栓对血管再通的影响。**方法** 共 92 例颅内大血管闭塞致急性缺血性卒中患者均行血管内治疗(包括导管抽吸、机械取栓、球囊扩张术和支架植入术),并对取出的血栓标本行病理学检查。**结果** 92 例患者中 81 例(88.04%)实现血管再通[脑梗死溶栓血流分级(TICI)≥2b 级];66 例(71.74%)取出血栓;63 例(68.48%)行血栓标本病理学检查,包括动脉粥样硬化血栓形成型(AT 型)26 例(41.27%)、心源性栓塞型 24 例(38.10%)、其他明确病因型 2 例(3.17%)以及不明病因型 11 例(17.46%)。26 例 AT 型患者中单纯血管内治疗 18 例(69.23%),血管内桥接治疗 8 例(30.77%);导管抽吸 1 例(3.85%),机械取栓 25 例(96.15%),其中单纯机械取栓 9 例(34.62%)、机械取栓联合球囊扩张术 3 例(11.54%)、机械取栓联合支架植入术 3 例(11.54%)、机械取栓联合球囊扩张术和支架植入术 10 例(38.46%);其中 4 例(15.38%)血栓标本含胆固醇结晶,含胆固醇结晶与不含胆固醇结晶患者机械取栓次数差异无统计学意义[2.50(2.00,3.00)次对 2(2,2)次; $Z = -1.155, P = 0.248$ ]。AT 型与非 AT 型患者血栓标本胆固醇结晶比例差异有统计学意义[15.38%(4/26)对 0/37, Fisher 确切概率法: $P = 0.025$ ],而术后实现血管再通与未实现血管再通患者血栓标本胆固醇结晶比例差异无统计学意义[3.77%(2/53)对 2/10, Fisher 确切概率法: $P = 0.115$ ]。**结论** 急性缺血性卒中患者血栓标本含胆固醇结晶的比例较低,但其对 AT 型的诊断具有特异性,而对术后血管再通无影响。

**【关键词】** 卒中; 脑缺血; 血栓切除术; 颅内血栓形成; 胆固醇结晶(非 MeSH 词)

## Analysis of cholesterol crystals in thrombi obtained from endovascular treatment of acute ischemic stroke

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**【Abstract】 Objective** To compare the difference of the rate of cholesterol crystals in thrombi obtained from patients of acute ischemic stroke with different etiologies and the effect of thrombi containing cholesterol crystals on vascular recanalization. **Methods** A total of 92 patients with acute ischemic stroke caused by intracranial large vascular occlusion underwent endovascular treatment, such as catheter suction, thrombectomy, balloon dilatation and stent implantation. Histopathological examinations of the retrieved thrombi were performed. **Results** Of 92 cases, 81 cases (88.04%) achieved recanalization [Thrombolysis in Cerebral Infarction (TICI) ≥ 2b]. Thrombi were retrieved in 66 cases (71.74%) and 63 cases (68.48%) performed pathological examinations, among whom 26 cases (41.27%) were atherothrombosis (AT), 24 cases (38.10%) were cardioembolism (CE), 2 (3.17%) were stroke of other determined etiology (SOD) and 11 cases (17.46%) were stroke of undetermined etiology (SUD). Among 26 AT cases, 18 cases (69.23%) accepted

doi:10.3969/j.issn.1672-6731.2018.05.011

基金项目:河南省医学科技攻关计划重点项目(项目编号:201502019);河南省科技发展计划项目(项目编号:142300410274)

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endovascular treatment and 8 cases (30.77%) accepted bridging therapy. One case (3.85%) underwent catheter suction, and 25 cases (96.15%) underwent thrombectomy, including thrombectomy alone in 9 cases (34.62%), thrombectomy combined with balloon dilatation in 3 cases (11.54%), thrombectomy combined with stent implantation in 3 cases (11.54%), thrombectomy combined with balloon dilatation and stent implantation in 10 cases (38.46%), respectively. Cholesterol crystals were detected in 4 cases (15.38%). There was no significant difference in the number of thrombectomy between thrombi with cholesterol crystals and those without cholesterol crystals [2.50 (2.00, 3.00) times vs. 2 (2, 2) times;  $Z = -1.155$ ,  $P = 0.248$ ]. Among 37 non-AT cases, 26 cases (70.27%) accepted endovascular treatment and 11 cases (29.73%) accepted bridging therapy. All of them underwent thrombectomy, including thrombectomy alone in 34 cases (91.89%), thrombectomy combined with balloon dilatation in one case (2.70%), thrombectomy combined with stent implantation in 2 cases (5.41%), respectively. There was statistically significant difference in the rate of cholesterol crystals between AT cases and non-AT cases [15.38% (4/26) vs. 0/37, Fisher's exact probability:  $P = 0.025$ ]. There was no significant difference in the rate of cholesterol crystals between patients with and without recanalization [3.77% (2/53) vs. 2/10, Fisher's exact probability:  $P = 0.115$ ]. **Conclusions** Although the rate of cholesterol crystals in thrombi of acute ischemic stroke patients is relatively low, it is specific for diagnosing AT. Besides, cholesterol crystals has no relationship with vascular recanalization.

**【Key words】** Stroke; Brain ischemia; Thrombectomy; Intracranial thrombosis; Cholesterol crystal (not in *MeSH*)

This study was supported by Key Medical Science and Technology Program of He'nan Province, China (No. 201502019) and Science and Technology Development Plan Project of He'nan Province, China (No. 142300410274).

脑卒中业已位居全球病死率第 2 位,是我国病残和病死的首位原因<sup>[1]</sup>。我国每年新发脑卒中患者  $250 \times 10^3$  例,而美国每年新发  $70 \times 10^3$  例<sup>[2]</sup>,其中缺血性卒中占 70%。闭塞动脉及时再通是最符合急性缺血性卒中病理生理学特点的治疗措施,晚近临床试验显示,血管内治疗可以显著提高血管再通率并改善临床预后<sup>[3-9]</sup>。血管内治疗使获得颅内血栓成为可能,而关于血栓成分的病理学<sup>[10-17]</sup>及其与改良 TOAST 分型<sup>[18]</sup>或其他相关因素之间关系的研究较少。颅内动脉粥样硬化性狭窄致缺血性卒中在东亚脑卒中患者中占 30%~50%<sup>[19]</sup>,理论上胆固醇结晶是动脉粥样硬化的特异性标志物,有助于病因诊断,而目前关于颅内血栓胆固醇结晶的研究罕见。本研究前瞻性单中心收集行血管内治疗的急性缺血性卒中患者的血栓标本,并对其成分进行病理学检查,比较不同改良 TOAST 分型患者血栓标本胆固醇结晶比例差异以及含胆固醇结晶的血栓对血管再通的影响。

## 资料与方法

### 一、临床资料

1. 纳入标准 (1) 经数字减影血管造影术 (DSA) 证实的颅内大血管闭塞致急性缺血性卒中。(2) 均行血管内治疗并获得可供病理学检查的颅内

血栓标本。(3) 本研究经河南省人民医院道德伦理委员会审核批准,所有患者或其委托人均知情同意并签署知情同意书。

2. 排除标准 (1) 小动脉闭塞致急性缺血性卒中患者。(2) 血管内治疗未取出血栓或血栓标本无法行病理学检查患者。

3. 一般资料 选择 2017 年 2-11 月在河南省人民医院进行血管内治疗的 92 例急性缺血性卒中患者,男性 61 例,女性 31 例;年龄 26~89 岁,平均  $(61.42 \pm 13.08)$  岁。

### 二、研究方法

1. 临床资料采集 分别详细记录患者性别、年龄、既往史(包括高血压、糖尿病、冠心病、心房颤动、高脂血症、脑卒中病史,吸烟史、饮酒史)和入院时美国国立卫生研究院卒中量表(NIHSS)评分,并由两位高级职称的临床医师独立采用改良 TOAST 分型进行病因分型,包括动脉粥样硬化血栓形成型(AT型)、心源性栓塞型(CE型)、其他明确病因型(SOD型)和不明病因型(SUD型),二者意见不一致时协商后达成共识。

2. 血管内治疗及血管再通评价 所有患者均经 16 层螺旋 CT 排除颅内出血,根据《中国急性缺血性脑卒中静脉溶栓指导规范(2016)》<sup>[20]</sup>,治疗时间窗内无禁忌证者首先予以重组组织型纤溶酶原激活

物(rt-PA)0.90 mg/kg 静脉溶栓,溶栓期间症状未减轻或加重以及超过治疗时间窗的患者,进一步行多模态 MRI 检查,观察梗死灶体积、缺血半暗带区体积和大血管受累情况,综合评价后由临床经验丰富的神经介入科医师进行血管内治疗,包括导管抽吸、机械取栓(Solitaire AB 支架,美国 Medtronic 公司)、球囊扩张术和支架植入术。术后采用脑梗死溶栓血流分级(TICI)<sup>[21]</sup>评价血管再通,TICI 分级 ≥ 2b 级为血管再通。

3. 血栓标本采集及病理学检查 取出血栓后采用佳能 EOS 77D 数码相机(日本 Canon 公司)采集标本图像,再将血栓标本固定于体积分数为 10% 中性甲醛溶液 1 d,再次采用数码相机采集标本图像,然后将血栓标本脱水、石蜡包埋,制备 5 μm 层厚切片,行 HE 染色。由两位病理科医师独立、双盲进行血栓标本病理学检查,于 Olympus BX43 型光学显微镜(日本 Olympus 公司)下观察,意见不一致时协商后达成共识。

4. 统计分析方法 采用 SPSS 21.0 统计软件进行数据处理与分析。计数资料以相对数构成比(%)或率(%)表示,采用χ<sup>2</sup>检验或 Fisher 确切概率法;呈正态分布的计量资料以均数 ± 标准差( $\bar{x} \pm s$ )表示,采用两独立样本的 *t* 检验;呈非正态分布的计量资料以中位数和四分位数间距 [*M*(*P*<sub>25</sub>, *P*<sub>75</sub>)] 表示,采用 Mann-Whitney *U* 检验。以 *P* ≤ 0.05 为差异具有统计学意义。

## 结 果

### 一、临床资料

92 例行血管内治疗的急性缺血性卒中患者中 81 例(88.04%)实现血管再通(TICI 分级 ≥ 2b 级),66 例(71.74%)取出血栓,63 例(68.48%)进行血栓标本病理学检查。男性 38 例,女性 25 例;年龄为 27 ~ 88 岁,平均(61.10 ± 12.50)岁;既往有高血压 35 例(55.56%)、糖尿病 27 例(42.86%)、冠心病 21 例(33.33%)、心房颤动 22 例(34.92%)、高脂血症 29 例(46.03%)、脑卒中病史 14 例(22.22%),吸烟 26 例(41.27%)、饮酒 20 例(31.75%);入院时 NIHSS 评分 2 ~ 36 分,中位评分 16(14, 20)分;根据改良 TOAST 分型,AT 型 26 例(41.27%),CE 型 24 例(38.10%),SOD 型 2 例(3.17%),SUD 型 11 例(17.46%);53 例(84.13%)实现血管再通。由于胆固醇结晶仅存在于 AT 型,且本研究 SOD 型病例数较少(仅 2 例),故

表 1 AT 型组与非 AT 型组患者一般资料的比较

Table 1. Comparison of general data between AT and non-AT patients

Item	AT (N=26)	Non-AT (N=37)	Statistic value	<i>P</i> value
Sex [case (%)]			2.323	0.128
Male	21 (80.77)	17 (45.95)		
Female	5 (19.23)	20 (54.05)		
Age ( $\bar{x} \pm s$ , year)	60.31 ± 10.20	61.65 ± 14.00	-0.416	0.679
Hypertension [case (%)]	17 (65.38)	18 (48.65)	1.732	0.188
Diabetes mellitus [case (%)]	13 (50.00)	14 (37.84)	0.922	0.337
Coronary heart disease [case (%)]	9 (34.62)	12 (32.43)	0.033	0.856
Atrial fibrillation [case (%)]	1 (3.85)	21 (56.76)	18.810	0.000
Hyperlipidemia [case (%)]	15 (57.69)	14 (37.84)	2.423	0.120
History of stroke [case (%)]	6 (23.08)	8 (21.62)	0.019	0.891
Smoking [case (%)]	12 (46.15)	14 (37.84)	0.436	0.509
Drinking [case (%)]	11 (42.31)	9 (24.32)	2.279	0.131
NIHSS [ <i>M</i> ( <i>P</i> <sub>25</sub> , <i>P</i> <sub>75</sub> ), score]	17 (14, 20)	16 (14, 19)	-0.652	0.514
Recanalization [case (%)]	20 (76.92)	33 (89.19)	1.720	0.190

Two - independent - sample *t* test for comparison of age, Mann - Whitney *U* test for comparison of NIHSS, and χ<sup>2</sup> test for comparison of others. AT, atherothrombosis, 动脉粥样硬化血栓形成; NIHSS, National Institutes of Health Stroke Scale, 美国国立卫生研究院卒中量表

将 CE 型、SOD 型和 SUD 型合并为非 AT 型进行统计分析。(1)AT 型:26 例患者,男性 21 例,女性 5 例;年龄 43 ~ 88 岁,平均(60.31 ± 10.20)岁;既往有高血压 17 例(65.38%)、糖尿病 13 例(50%)、冠心病 9 例(34.62%)、心房颤动 1 例(3.85%)、高脂血症 15 例(57.69%)、脑卒中病史 6 例(23.08%),吸烟 12 例(46.15%)、饮酒 11 例(42.31%);入院时 NIHSS 评分 4 ~ 36 分,中位评分 17(14, 20)分;20 例(76.92%)实现血管再通。(2)非 AT 型:37 例患者,男性 17 例,女性 20 例;年龄 27 ~ 83 岁,平均(61.65 ± 14.00)岁;既往有高血压 18 例(48.65%)、糖尿病 14 例(37.84%)、冠心病 12 例(32.43%)、心房颤动 21 例(56.76%)、高脂血症 14 例(37.84%)、脑卒中病史 8 例(21.62%),吸烟 14 例(37.84%)、饮酒 9 例(24.32%);入院时 NIHSS 评分 2 ~ 36 分,中位评分 16(14, 19)分;33 例(89.19%)实现血管再通。两组患者一般资料比较,仅心房颤动差异有统计学意义(χ<sup>2</sup> = 18.810, *P* = 0.000),其余各项指标差异均无统计学意义(*P* > 0.05, 表 1)。

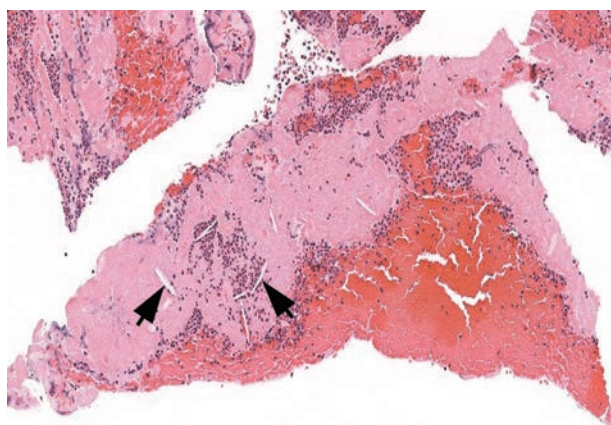


图 1 光学显微镜观察显示,血栓内含胆固醇结晶(箭头所示) HE 染色 ×200

Figure 1 Optical microscopy findings showed cholesterol crystals in thrombus (arrows indicate). HE staining ×200

表 2 AT 型组与非 AT 型组患者血栓标本胆固醇结晶比例的比较[例(%)]

Table 2. Comparison of rate of cholesterol crystals in thrombi between AT and non-AT patients [case (%)]

Group	N	Cholesterol crystal	P value*
AT	26	4 (15.38)	0.025
Non-AT	37	0 ( 0.00)	

\*Fisher's exact probability, Fisher 确切概率法。AT, atherothrombosis, 动脉粥样硬化血栓形成

表 3 术后实现血管再通与未实现血管再通患者血栓标本胆固醇结晶比例的比较[例(%)]

Table 3. Comparison of the rate of cholesterol crystals in thrombi between patients with and without recanalization [case (%)]

Group	N	Cholesterol crystal	P value*
Recanalization	53	2 (3.77)	0.115
Non-recanalization	10	2 (2/10)	

\*Fisher's exact probability, Fisher 确切概率法

## 二、血管内治疗

63 例患者中单纯血管内治疗 44 例(69.84%), 血管内桥接治疗 19 例(30.16%); 导管抽吸 1 例(1.59%), 机械取栓 62 例(98.41%), 其中单纯机械取栓 43 例(68.25%)、机械取栓联合球囊扩张术 4 例(6.35%)、机械取栓联合支架植入术 5 例(7.94%)、机械取栓联合球囊扩张术和支架植入术 10 例(15.87%)。病理学检查显示, 4 例(6.35%)取出含胆固醇结晶的血栓, 1 例行机械取栓联合球囊扩张术、3 例行机械取栓联合球囊扩张术和支架植入术。血栓标本含胆固醇结晶的患者机械取栓次数 2~3 次、

中位值 2.50(2.00, 3.00)次, 血栓标本不含胆固醇结晶的患者机械取栓次数 1~6 次、中位值 2.00(1.25, 3.00)次, 组间差异未达到统计学意义( $Z = -0.845, P = 0.398$ )。(1)AT 型: 26 例患者中单纯血管内治疗 18 例(69.23%), 血管内桥接治疗 8 例(30.77%); 导管抽吸 1 例(3.85%), 机械取栓 25 例(96.15%), 其中单纯机械取栓 9 例(34.62%)、机械取栓联合球囊扩张术 3 例(11.54%)、机械取栓联合支架植入术 3 例(11.54%)、机械取栓联合球囊扩张术和支架植入术 10 例(38.46%)。病理学检查显示, 4 例(15.38%)取出含胆固醇结晶的血栓, 1 例行机械取栓联合球囊扩张术、3 例行机械取栓联合球囊扩张术和支架植入术。血栓标本含胆固醇结晶的患者机械取栓次数 2~3 次、中位值 2.50(2.00, 3.00)次, 血栓标本不含胆固醇结晶的患者机械取栓次数 1~4 次、中位值 2(2, 2)次, 组间差异无统计学意义( $Z = -1.155, P = 0.248$ )。(2)非 AT 型: 37 例患者中单纯血管内治疗 26 例(70.27%), 血管内桥接治疗 11 例(29.73%); 均采用机械取栓, 其中单纯机械取栓 34 例(91.89%)、机械取栓联合球囊扩张术 1 例(2.70%)、机械取栓联合支架植入术 2 例(5.41%)。

## 三、血栓成分及血栓标本胆固醇结晶比例

取出的血栓主要由红细胞、纤维蛋白、血小板和白细胞组成。本组有 4 例患者血栓标本含胆固醇结晶(图 1), 均为 AT 型, 而 CE 型、SOD 型和 SUD 型患者均未检出血栓标本含胆固醇结晶, 组间差异有统计学意义(Fisher 确切概率法:  $P = 0.025$ , 表 2)。53 例术后实现血管再通(TICI 分级  $\geq 2b$  级)的患者中 2 例(3.77%)血栓标本含有胆固醇结晶, 10 例未实现血管再通(TICI 分级  $\leq 2a$  级)的患者中 2 例(2/10)血栓标本含有胆固醇晶体, 组间差异无统计学意义(Fisher 确切概率法:  $P = 0.115$ , 表 3)。

## 讨 论

迄今仅少量文献对急性缺血性卒中的颅内血栓成分进行病理学研究, 且研究结果多不一致, 提示急性缺血性卒中的颅内血栓成分具有高度异质性<sup>[10]</sup>。大部分血栓由红细胞、纤维蛋白、血小板和白细胞组成, 亦有个别栓子含其他成分, 如本研究急性缺血性卒中患者血栓标本病理学检查可见胆固醇结晶(4 例, 6.35%), 而 Marder 等<sup>[10]</sup>、

Almekhlafi 等<sup>[11]</sup>和 Kim 等<sup>[14]</sup>均未发现胆固醇结晶,可能与他们纳入的 AT 型患者病例数较少有关,分别为 4、5 和 8 例。胆固醇结晶是动脉粥样硬化的特异性标志物,提示其病因分型为 AT 型。本研究仅 AT 型患者血栓标本含胆固醇结晶,且不同改良 TOAST 分型患者血栓标本胆固醇结晶比例差异有统计学意义亦证实这一观点。

然而, Masuda 等<sup>[22]</sup>对 15 例 AT 型患者进行尸体解剖,仅 1 例颅内大血管(右侧颈内动脉末端)闭塞患者血栓标本含大量胆固醇结晶,余 14 例中 13 例仅在颅内小血管如软脑膜动脉(直径 < 300  $\mu\text{m}$ )和左侧大脑后动脉分支(直径约 800  $\mu\text{m}$ )发现胆固醇结晶,表明含胆固醇结晶的血栓往往堵塞颅内小血管,而这些血管目前尚无法进行血管内治疗,因此并非所有 AT 型患者颅内大血管血栓标本均可以检出胆固醇结晶,本研究 26 例 AT 型患者中 4 例(15.38%)血栓标本含胆固醇结晶,与 Masuda 等<sup>[22]</sup>的研究结果相一致。Ogata 等<sup>[23]</sup>对急性缺血性卒中患者进行尸体解剖,发现主要由胆固醇结晶组成的血栓易闭塞远端小血管,从而诱发分水岭梗死,而富含纤维蛋白和血小板并包含胆固醇结晶的血栓易闭塞较大血管,且主要由纤维蛋白松散网罗胆固醇结晶组成的栓子易分裂为较小碎片。

Hashimoto 等<sup>[15]</sup>认为,含动脉粥样硬化样物质的血栓与脑组织再灌注失败有关,此类血栓易破碎的物理特性可能降低血栓切除术的有效性,与本研究结果不同。本研究结果显示,术后实现血管再通与未实现血管再通患者血栓标本胆固醇结晶比例差异无统计学意义,提示含胆固醇结晶的血栓堵塞的血管并不一定再通困难。本研究结果还显示,血栓标本含胆固醇结晶与不含胆固醇结晶的患者机械取栓次数差异无统计学意义,进一步比较血栓标本含胆固醇结晶与不含胆固醇结晶的 AT 型患者机械取栓次数,差异亦无统计学意义,结合临床实际以及目前最新的机械取栓技术和设备,表明含胆固醇结晶的血栓并不增加机械取栓的难度。究其原因,可能与笔者所在河南省人民医院采用的机械取栓装置、技术的革新和多种手术方法的联合应用有关,且本研究在短期(10 个月)内采用同一种支架(Solitaire AB 支架)进行机械取栓,与其他已发表的跨度达数年的临床研究不同,如 Marder 等<sup>[10]</sup>的研究时间跨度为 3 年 10 个月,并采用不同机械取栓装置和技术,使获得的血栓标本成分更有异质性。

本研究尚存在以下局限性:首先,本研究是单中心回顾性分析,但数据的采集是前瞻性的,可以最大限度地降低回顾性研究的选择偏倚;其次,本研究样本量较小;再次,机械取栓装置可以影响血栓的完整性或仅取出部分血栓,从而影响病理学检查结果;最后,未取出血栓的患者无法进行病理学检查,故不能反映所有颅内大血管闭塞致急性缺血性卒中的血栓病理学情况。

## 结 论

本研究急性缺血性卒中患者血栓标本含胆固醇结晶的比例较低,但其对 AT 型的诊断具有特异性,而对术后血管再通无影响。

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(收稿日期:2018-04-30)

**下期内容预告** 本刊2018年第6期报道专题为儿童和青少年癫痫,重点内容包括:青少年癫痫诊断与治疗进展;结节性硬化症遗传学研究及诊断与治疗进展;癫痫表观遗传学研究进展;癫痫急性症状性发作临床研究进展;丙戊酸钠对儿童癫痫患者骨密度和骨代谢的安全性评价;儿童和青少年癫痫相关局灶性皮质发育不良22例临床分析;易误诊为局灶性皮质发育不良Ⅱb型的结节性硬化症之皮质结节临床病理学特征;早期癫痫性脑病临床表型和基因突变特征及二代基因测序在病因诊断中的应用;奥卡西平活性代谢产物测定在儿童局灶性癫痫治疗中的应用