

# 非瓣膜性心房颤动患者导管消融术后抗凝策略的研究进展

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**【摘要】** 非瓣膜性心房颤动患者导管消融术后的卒中预防策略尚存争议, 现有指南大多推荐根据 CHA<sub>2</sub>DS<sub>2</sub>-VASc 评分制定抗凝策略, 建议 CHA<sub>2</sub>DS<sub>2</sub>-VASc 评分  $\geq 2$  分的卒中高风险患者术后长期抗凝。但目前临床实践中, 抗凝出血风险和患者依从性等问题仍待解决, 对心房颤动患者术后卒中来源的剖析、卒中风险的全面评估以及个体化卒中预防策略的制定等问题仍有待进一步研究, 现结合最新研究进展和观点对此问题展开综述。

**【关键词】** 非瓣膜性心房颤动; 导管消融; 卒中; 抗凝药物

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## Anticoagulation Strategy in Patients with Nonvalvular Atrial Fibrillation after Catheter Ablation

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**【Abstract】** The prevention strategies of stroke in patients with non-valvular atrial fibrillation after catheter ablation are still controversial. Most existing guidelines recommend that anticoagulation strategies should be formulated according to CHA<sub>2</sub>DS<sub>2</sub>-VASc score, and the patients whose CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  should receive long-term anticoagulation after ablation. However, the problems such as bleeding risk of anticoagulants and compliance of patients in clinical practice still need to be solved. It is still need to be further studied that the analysis on the source of stroke, the comprehensive assessment of stroke risk, and the formulation of individual stroke prevention strategies in atrial fibrillation patients after ablation. This paper will review this issue with the latest research progress and perspectives.

**【Key words】** Non-valvular atrial fibrillation; Catheter ablation; Stroke; Anticoagulants

心房颤动(房颤)是临床常见的心律失常,截至2010年,全球患病人数约3 350万。据报道,约28%的缺血性卒中与房颤相关,卒中预防是房颤管理的重要部分。对于不合并中重度二尖瓣狭窄或机械性人工心脏瓣膜的非瓣膜性房颤患者,导管消融相比抗心律失常药物具有更高的窦性心律维持率和更低的死亡率,尽管有研究指出导管消融也能降低卒中发生率<sup>[1]</sup>,但其远期效果可能仍劣于口服抗凝药物(oral anticoagulants, OACs)<sup>[2]</sup>;此外,导管消融尚存在一定的远期复发率(包括无症状发作)。因此,对于CHA<sub>2</sub>DS<sub>2</sub>-VASc评分 $\geq 2$ 分的房颤患者,欧美指南均不推荐以导管消融替代抗凝治疗。然而另有研究显示,在导管消融3个月后,患者继续或停止抗凝治疗的栓塞发生率均较低且无显著差异,但抗凝治疗会增加出血风险<sup>[3]</sup>。目前,非瓣膜性房颤患者导管消

融术后卒中风险的精准评估和个体化抗凝策略的制定尚无定论。

### 1 导管消融术后长期抗凝的观点和证据

#### 1.1 术后窦性心律维持率和有效监测率低

既往有研究表明,房颤患者接受标准药物治疗的卒中发病率为2.8/100人年,接受导管消融且长期维持窦性心律的患者卒中发病率则为0.5/100人年;而在不使用OACs前提下,以14 d长程心电监测定义的房颤高负荷患者(监测期内房颤总持续时长/监测时长 $\geq 11.4\%$ )缺血性卒中风险是房颤低负荷组的3倍<sup>[4]</sup>。因此,只有术后长期维持窦性心律的患者才真正具有卒中低风险。尽管消融技术在进步,但若以14 d长程心电监测进行评估,阵发性房颤患者术后9年的无复发率为66%;而对于持续性或长程持续性房颤患者,单次消融术后25个月的无复发率为

43%<sup>[5]</sup>。另一方面,在房颤人群中,无症状患者的比例为 10%~40%,且消融术后部分患者的症状感受会更加轻微且不易监测,因此在缺乏长程监测手段的情况下,术后停止抗凝治疗或许会增加血栓栓塞(thromboembolism, TE)风险。

## 1.2 房颤患者合并症多且卒中风险高

据统计,全球 90.7% 的卒中与高血压、糖尿病、血脂异常、吸烟、饮酒和肥胖等因素相关,而房颤患者合并慢性病的比例较高,其中合并高血压的比例为 83.2%,且诊断房颤前,高血压病程>3 年即是缺血性卒中的危险因素<sup>[6]</sup>;而合并糖尿病则使卒中风险相对增加 70%<sup>[7]</sup>;此外,血清总胆固醇、低密度脂蛋白胆固醇和甘油三酯水平均与缺血性卒中呈正相关<sup>[8]</sup>。理论上讲,导管消融并维持窦性心律有助于降低心源性卒中风险,但慢性病患者的动脉粥样硬化

(atherosclerosis, AS) 危险因素仍是房颤患者术后卒中风险的来源,需进行有效管理。

## 1.3 心房基质可能是血栓形成最重要的影响因素

既往研究发现房颤发作与卒中发生存在时间上分离的现象,也就是说,并非房颤而是心房基质才是导致血栓形成的重要原因<sup>[9]</sup>,即各种疾病和理化因素导致心房心肌病,形成血栓前状态,进而引发 TE 事件<sup>[10]</sup>。近期 Bisbal 等<sup>[11]</sup>提出“心房衰竭”概念,认为由解剖、机械、电生理和/或血流动力学异常引起的心房功能障碍,可导致包括卒中在内的一系列临床事件;房颤更可能是心房心肌病的表现,而非血栓形成的诱因(图 1),因此房颤患者术后是否需长期抗凝治疗不能仅由心律决定,而需全面评估患者的心房结构和功能。

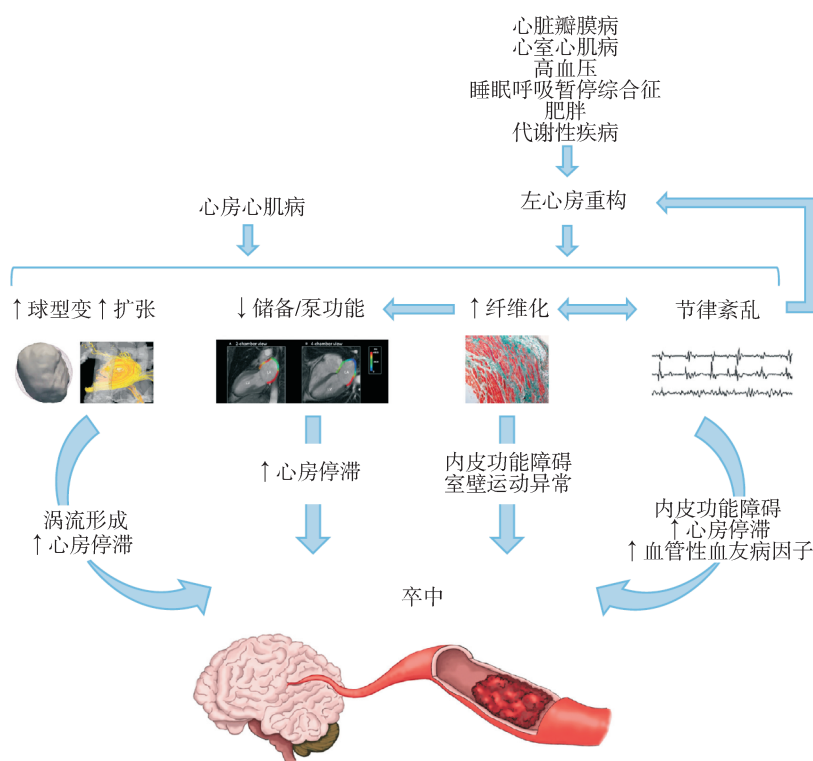


图 1 心房衰竭患者卒中的病理生理学机制<sup>[11]</sup>

## 1.4 术后患者心脏结构和功能逆重构过程漫长

房颤连同诸多危险因素可引起心房重构,造成心功能下降,即“房颤介导性心肌病”。即使恢复窦性心律后心脏功能或可在短期内改善,但心脏重构可能持续相对漫长且部分不可逆<sup>[12]</sup>,且一旦复发,心脏功能会迅速恶化。而房颤患者左房储备功能受损显著增加短暂性脑缺血发作(transient ischemic attack, TIA)和卒中发生率<sup>[13]</sup>,因此房颤患者术后抗凝时间过短可能会增加卒中风险。

## 2 长期抗凝的风险和现实问题

### 2.1 长期抗凝可能无临床获益甚至增加出血事件

丹麦一项研究<sup>[3]</sup>显示,非瓣膜性房颤患者消融术后停用或不停用 OACs 的 TE 发生率分别为 0.56/100 人年和 0.64/100 人年,而抗凝组严重出血发生率更高。尽管非维生素 K 拮抗剂类 OACs 致命性大出血风险低于华法林,但以利伐沙班为例,ROCKET AF 研究结果显示其全部临床相关出血事件发生率为 14.9/100 人年,且对部分高出血风险患者,OACs 的应用更

加受限。

## 2.2 真实世界中 OACs 使用率低且依从性差

GLORIA-AF 研究<sup>[14]</sup>显示,目前全球范围内 CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub>评分 $\geq 2$ 分的非瓣膜性房颤患者约占所有患者的 86.1%,而接受 OACs 治疗的患者为 79.9%。相比欧洲和北美等地区,亚洲地区缺乏有效抗凝治疗的患者比例更高,较华法林更便捷的非维生素 K 拮抗剂类药物在真实世界中的用药依从性同样不高。以达比加群为例,多数研究报道其用药依从性为 56.5%~76.8%<sup>[15]</sup>,而华法林在中国人群中 1 年停药率为 44.4%<sup>[16]</sup>,抗凝引发出血可能使停药率进一步增加。

## 3 房颤患者卒中风险评价系统有待完善

### 3.1 CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub>评分

近期研究报道消融术后房颤负荷可降低约 99%<sup>[17]</sup>,卒中风险也随之降低,对 CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub>评分 0~1 分的非瓣膜性房颤患者,或可在严密监测下停止长期抗凝治疗,而此部分具有中低危卒中风险的房颤患者随年龄增长,其 CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub>评分的年增长率接近 12%,因此推荐每隔 3~4 个月进行卒中风险再评估并适时启动抗凝治疗<sup>[18]</sup>。随 CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub>评分增加,房颤患者卒中发生率逐渐升高,既往研究指出,CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub>评分为 4 分的房颤患者,在无抗凝保护下的卒中发生率为 5.45/100 人年,而 CHA<sub>2</sub>DS<sub>2</sub>-

VAS<sub>c</sub>评分 $\geq 4$ 分的无房颤人群的卒中发生率也超过 0.9/100 人年<sup>[19]</sup>,年龄 $>75$  岁者卒中发生率为 2.47/100 人年<sup>[20]</sup>。依据 CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub>评分采用 OACs,对高危患者实施抗凝治疗可使卒中发生率下降 59.3%~71.6%,且评分越高其卒中绝对风险降低越显著<sup>[21]</sup>,因此对 CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub>评分 $\geq 4$ 分的非瓣膜性房颤患者,即使消融术后长期维持窦性心律,也应长期抗凝。此外,CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub>评分系统所纳入的卒中危险因素多局限于临床病史,已有研究表明在其基础上加入其他预测因素可提高卒中的预测价值<sup>[22-23]</sup>。

### 3.2 左心结构和功能评价

Cresti 等<sup>[24]</sup>对 1 420 例房性心律失常患者进行经食管超声心动图检查(transesophageal echocardiography, TEE),发现心腔内血栓发生率为 6.13%,95.6%的血栓位于左心耳。既往报道,相比左心耳血栓,TEE 发现左心耳内自发回声显影的比例更高,且其与 TE 显著相关。左心耳的排空受到左心房结构和血流动力学影响,低左心耳排空速率( $<47$  mL/s)与高左心房压力独立相关<sup>[25]</sup>,而左心房扩大也可增加血栓及卒中风险<sup>[26]</sup>。此外,左心室的结构和功能同样对房颤患者心腔内血栓形成及卒中风险产生影响,通过心脏超声或其他手段对左心结构和功能的全面评价有助于评估卒中风险(表 1)。

表 1 与房颤患者卒中相关的左心结构与功能评价指标

发表年份	研究者	研究指标	主要结论
2016	Lupercio 等	左心耳形态	鸡翅型左心耳较非鸡翅形态 TE 风险降低 54%。
2013	Khurram 等	左心耳内部结构	左心耳小梁范围广和开口直径小与 TE 独立相关。
2014	Nedios 等	左心耳开口位置	左心耳开口高于左上肺静脉开口,增加卒中风险。
2013	Doukky 等	左心房容积	左心房容积指数是左心耳血栓的独立预测因子。
2017	King 等	左心房纤维化	左心房严重纤维化增加卒中和 TIA 的发生率。
2013	Boyd 等	左心室质量指数	左心室质量指数是持续性房颤患者左心耳血栓的独立预测因子。
2016	Garcia-Sayan 等	左心室舒张功能	二尖瓣环侧壁 E/e' $\geq 8$ ,预测左心耳血栓敏感性为 100%,特异性为 41%。

### 3.3 可预测卒中风险的生物标志物

部分心血管疾病相关生物标志物也与房颤患者卒

中有关,可用以联合评估患者卒中风险(表 2)。

表 2 针对房颤患者卒中相关临床化验指标的研究

发表年份	研究者	研究指标	参考截点	主要结论
2018	Yao 等	Hcy	Hcy $\geq 13.5$ mmol/L	CHA <sub>2</sub> DS <sub>2</sub> -VAS <sub>c</sub> 评分 0~1 分患者,Hcy 升高增加左心房/左心耳血栓形成风险。
2019	Choi 等	D-二聚体	D-二聚体 $>2$ $\mu$ g/mL	高 D-二聚体水平与房颤相关卒中复发高风险相关。
2018	Hayashi 等	BNP	BNP $>147$ pg/mL	BNP 升高增加 TE 和全因死亡风险。
2014	Hijazi 等	hs-TnI	hs-TnI $\geq 3.3$ ng/L	高 hs-TnI 与卒中、心源性死亡和大出血风险升高独立相关。
2015	Saliba 等	GHb	GHb $\geq 7.0\%$	GHb 水平与卒中风险呈正相关。

注:Hcy:同型半胱氨酸;BNP:脑钠肽;hs-TnI:超敏肌钙蛋白 I;GHb:糖化血红蛋白。

## 4 房颤患者术后卒中风险控制策略

### 4.1 提升消融手术远期成功率

房颤导管消融术后复发的原因之一,是肺静脉外触发灶未被干预, Lim 等<sup>[27]</sup>对非阵发性房颤患者进行非侵入式体表标测,发现在左心耳区域标测到局灶性或折返性触发灶的患者分别占 50% 和 55%。目前国内许多中心在肺静脉隔离的基础上进行左心耳电隔离术,荟萃分析显示在停用抗心律失常药物的前提下,随访 12 个月,左心耳电隔离术治疗组无房颤复发率为 75.5%,而标准消融组(对照组)为 43.9%<sup>[28]</sup>。在安全性方面,左心耳电隔离术组缺血性卒中发生率与对照组无差异,左心耳电隔离术或可降低术后复发率而不增加卒中风险。然而近期多项研究表明,左心耳电隔离术影响左心耳收缩功能进而增加卒中或 TIA 发生率<sup>[29-30]</sup>,因此目前主张左心耳电隔离术患者应长期应用 OACs 预防卒中;而左心耳电隔离术后进一步进行左心耳封堵术或可作为预防卒中的另一种策略。Gadiyaram 等<sup>[31]</sup>对 162 例左心耳电隔离术后成功置入封堵器的患者随访,45 d 时 TEE 检查发现 2 例封堵器周围漏(>5 mm),此时 OACs 停药率为 92.6%,且该部分患者后续随访无 TE 事件,证实在左心耳电隔离术后进行左心耳封堵安全可行。

### 4.2 术后房颤复发监测手段逐渐精准便捷

由于存在大量无症状房颤发作,以临床症状和不连续监测手段指导消融术后抗凝策略不恰当。长程动态心电图能提高房颤检出率,且延长监测时间可再度提高诊断率。可定期监测的手持式心电装置在监测房颤复发方面同样具有较高的诊断敏感度,且具有无创、简便和低廉的优势<sup>[32]</sup>,而腕表式设备可长程监测心律,且报告房颤发作的准确率>96%<sup>[33]</sup>。随着目前心电监测设备的逐渐优化,未来对房颤术后复发的监测也将更加精准。

### 4.3 控制患者术后复发和卒中相关危险因素

房颤患者需综合管理,研究显示多个临床可干预的危险因素与房颤发作及卒中等并发症有关,对血压、血糖和血脂的有效控制以及对睡眠呼吸暂停和慢性阻塞性肺病等相关疾病的治疗能降低术后复发率;而改变静坐为主的生活方式,控制肥胖同样有益,最近报道戒酒也能降低房颤负荷及复发风险<sup>[34]</sup>。

### 4.4 术后卒中预防的抗血小板治疗策略

华法林在房颤患者心源性栓塞预防方面优于单药甚至联合抗血小板治疗,但缺血性卒中病因复杂(图 2)<sup>[35]</sup>。最近研究报道在应用非维生素 K 拮抗剂类治疗的非瓣膜性房颤患者中,由原位血管病变及其他病因导致的卒中占 32.7%<sup>[36]</sup>,而 OACs 对此部分卒中预防价值不及抗血小板药物,故美国指南推荐抗血小板

药物用作合并 AS 的缺血性卒中/TIA 患者的二级预防;在预防不明原因栓塞性卒中复发方面,以达比加群为代表的 OACs,疗效并不优于阿司匹林,且出血事件增多<sup>[37]</sup>;因此,对于有缺血性卒中史合并血管病变等其他卒中相关原发病,而心源性栓塞风险低的房颤患者,在消融术后维持窦性心率的前提下,以长期抗血小板药物替换 OACs 预防卒中可能更为获益。

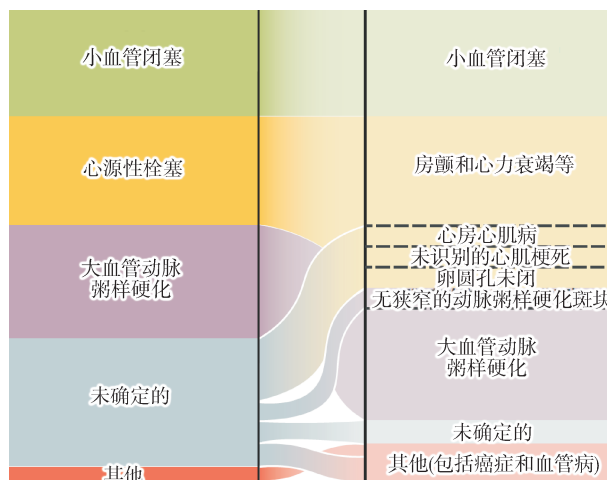


图2 缺血性卒中发病机制和分类<sup>[35]</sup>

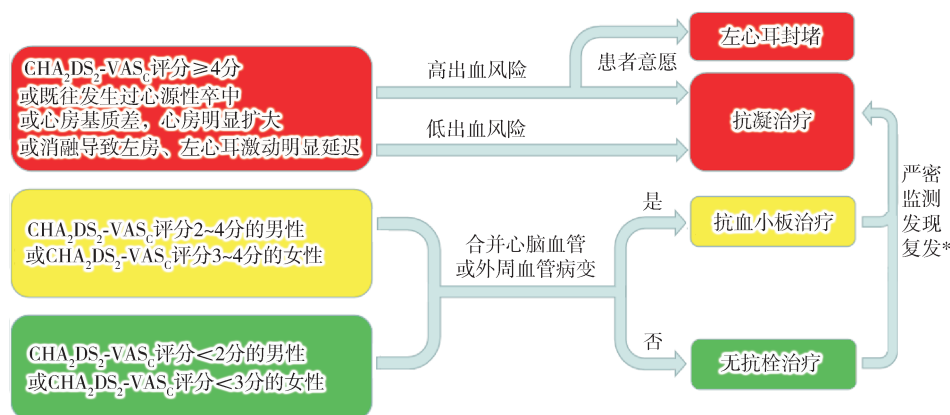
对于经皮冠脉介入术治疗后的房颤患者,目前证据倾向缩短 OACs 联合双联抗血小板药物治疗时程,推荐在经皮冠脉介入术后 1 年单联 OACs 治疗<sup>[38]</sup>,房颤合并稳定性冠心病患者的标准剂量单联 OACs 的有效性及安全性亦优于联合抗血小板药物治疗<sup>[39]</sup>;而近期 COMPASS 研究及其亚组分析结果显示,小剂量利伐沙班联合阿司匹林的抗栓策略虽增加出血风险,但对 AS 患者,该方法较单药阿司匹林能进一步降低心源性和不明原因栓塞性卒中的发生率<sup>[40-41]</sup>,因此,对于合并冠状动脉/外周 AS 的低出血风险房颤患者,或许术后联合抗栓会更加获益。

### 4.5 如何个体化选择抗栓策略(本中心经验)

本中心根据每个患者的危险因素评估,结合自身经验,制定个体化抗栓策略(图 3)。

## 5 小结及展望

目前针对非瓣膜性房颤患者导管消融术后是否停用抗凝治疗仍缺乏大型研究证据,现阶段仍以 CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub>评分作为术后抗凝策略选择的重要依据;而房颤患者卒中/TE 来源复杂,需细化评估体系以制定个体化的抗栓策略,通过影像学等手段对患者心脏结构和功能的评估有助于预测卒中。未来消融术式的改良以及消融器材的更新将有助于提高消融成功率,术后检测设备的发展同样引人关注,期待更多研究证据涌现以指导房颤患者术后抗凝策略的选择。



注: \* :若房颤复发后发作负荷低,则发作短期内应用快速起效的非维生素 K 拮抗剂抗凝并持续至无发作后 1 个月;若房颤发作负荷重或呈持续性,则恢复长期抗凝。

图 3 非瓣膜性房颤患者术后抗栓策略选择(本中心经验)

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