·专题综述·

心房颤动相关性缺血性卒中临床研究现状

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【摘要】 心房颤动是急性缺血性卒中的独立危险因素，由其引起的缺血性卒中约占全部缺血性卒中的20%；与心房颤动相关的危险因素包括高龄（≥75岁）、高血压、糖尿病、近期心力衰竭、缺血性卒中或短暂性脑缺血发作病史，风险评价体系包括$CHADS_2$和CHA_2DS_2-$VASc$评分系统。风险评价体系的建立有利于评价脑卒中风险、决定采取何种治疗措施。预防性治疗原则为高度和中度风险行抗凝治疗、低度风险行抗血小板治疗或不治疗。华法林目前仍是主要抗凝药物，新型口服抗凝药虽具有脑卒中发生率和出血率低、无需监测等优点，但缺乏多中心大样本随机对照试验的验证。

【关键词】 卒中；　心房颤动；　血小板聚集抑制剂；　抗凝药；　综述

Clinical research status of atrial fibrillation related ischemic stroke

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【**Abstract**】 Atrial fibrillation (AF) is the independent risk factor for acute ischemic stroke. AF-related ischemic stroke account for 20% of total ischemic stroke. Risk factors include old age (≥ 75 years), hypertension, diabetes mellitus, recent heart failure, ischemic stroke and transient ischemic attack (TIA) history. Risk evaluation system mainly contains $CHADS_2$ and CHA_2DS_2-VASc. The establishment of risk evaluation system is favorable for evaluating the future risk of stroke, and deciding to take which kind of treatment measures: anticoagulant therapy for high, moderate risk; anti-platelet aggregation treatment or no treatment for low risk. Warfarin is still the main anticoagulant drug at present. New oral anticoagulants (NOACs) have advantages such as low incidence of stroke, low bleeding rate, no need to monitor, however, they are lack of validation from multicenter, large sample randomized controlled trials.

【**Key words**】 Stroke;　Atrial fibrillation;　Platelet aggregation inhibitors;　Anticoagulants;　Review

欧美人群心房颤动患病率为1%～2%，80岁以上人群为5%～15%[1]。Piccini等[2]认为，心房颤动的主要风险是全身性血栓栓塞。Roger等[3]提出，心房颤动是缺血性卒中的独立危险因素。心房颤动与缺血性卒中的密切关系不仅表现在脑血管病患者心房颤动患病率明显增加，而且心房颤动相关性缺血性卒中发生率较高。一项对纳入5038例缺血性卒中患者的32项临床研究的分析显示，新发心房颤动发生率为11.50%，其中隐源性卒中或发病前明确有心房颤动的缺血性卒中患者新发心房颤动的发生率为15.90%[4]。Komatsu等[5]开展的回顾性研究显示，未经治疗的阵发性心房颤动相关性缺血性卒中的年发生率为2.67%。Schirmer等[6]的研究提示，心房颤动相关性缺血性卒中占所有缺血性卒中的20%。Hannon等[7]发现，约有1/3的缺血性卒中与心房颤动有关。Schwammenthal等[8]认为，心房颤动相关性缺血性卒中近期和远期病死率均较高。中国国家卒中登记（CNSR）资料显示，经治疗的非瓣膜性心房颤动相关性缺血性卒中的1年病死率为34%[9]。因此，加强心房颤动及其相关性缺血性卒中的研究迫在眉睫。近年来，关于心房颤动及其相关性缺血性卒中的研究已经获得显著进展，24小时动态心电监测被推荐作为最主要的临床检查项目（Ⅰ级推荐）[10]。隐源性卒中及潜在心房颤动（CRYSTAL-AF）试验显示，应用植入式心脏监测器（ICM）的阳性检出率为30%，应用标准监测手段为3%，ICM可使心房颤动阳性检出率提高10倍[11]。美国神经病学学会（AAN）制定的新型口服抗凝药

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(NOACs)治疗指南公布[12],NOACs因较华法林更有效、更安全而在抗凝治疗中得到广泛认同。但是,目前已取得的研究成果距离研究目标还有很大差距,相信,随着科学技术的进步,心房颤动相关性缺血性卒中的研究一定会获得更大成果。

一、发生率和复发率

Schwamm等[13]研究显示,短暂性脑缺血发作(TIA)和缺血性卒中合并心房颤动的发生率为28%。中国国家卒中登记资料表明,经治疗的非瓣膜性心房颤动相关性缺血性卒中的1年复发率为32%[9]。2011年,Goldstein等[14]对2010年美国心脏协会(AHA)/美国卒中协会(ASA)脑卒中一级预防指南中的相关资料进行汇总,$CHADS_2$评分为零、1、≥2分的心房颤动患者脑卒中年发生率分别为0.50%~1.70%、1.20%~2.20%和1.90%~7.20%。Olesen等[15]的研究显示,$CHADS_2$评分为零,同时CHA_2DS_2-VASc评分为零、3分的脑卒中年发生率分别为0.84%和3.20%,$CHADS_2$评分0~1分,同时CHA_2DS_2-VASc评分1、2、3、4分的脑卒中年发生率分别为1.79%、3.67%、5.75%、8.18%。

二、危险因素

Lip等[16]指出,年龄65~74岁、血管性疾病史(心肌梗死、周围动脉病)和女性是心房颤动相关性缺血性卒中的危险因素。Yazdan-Ashoori和Baranchuk[17]认为,阻塞性睡眠呼吸暂停综合征(OSAS)是心房颤动相关性缺血性卒中的危险因素。Song等[18]的研究发现,脑微出血灶及其数目与非瓣膜性心房颤动相关性缺血性卒中的危险因素评分呈显著相关,而且评分越高,发生非瓣膜性心房颤动相关性缺血性卒中的可能性越大。目前已达成共识,高龄(≥75岁)、高血压、糖尿病、近期心力衰竭、缺血性卒中或短暂性脑缺血发作病史是心房颤动相关性缺血性卒中的危险因素。

三、危险因素评价体系

为了综合评价这些危险因素,以便对心房颤动相关性缺血性卒中进行预测和治疗,脑卒中风险分层方案应运而生。脑卒中风险分层方案通过对危险因素评分,以预测脑卒中的发生风险,评分低者发生脑卒中的风险低,称为低危;反之,称为高危;二者之间,称为中危。

$CHADS_2$是根据充血性心力衰竭(C)、高血压(H)、年龄(A)、糖尿病(D)、脑卒中(S)或短暂性脑缺血发作病史(S)来确定心房颤动相关性缺血性卒中风险的一种评价体系,Hong等[19]将$CHADS_2$评分0~1分定义为低危、2~3分定义为中危、≥4分定义为高危。2011年加拿大心血管病学会指南将$CHADS_2$评分为零定义为低危、1分为中危、≥2分为高危[20]。

CHA_2DS_2-VASc是在$CHADS_2$上述5项危险因素基础上,加入血管性疾病史、年龄(65~74岁)、性别(女性)3项危险因素而建立的一种评价体系。在CHA_2DS_2-VASc评价体系中新加入的3项危险因素各评为1分,如果年龄≥75岁则评为2分[10]。

Berisha等[21]指出,$CHADS_2$在辨别心房颤动相关性卒中低度和重度风险方面存在局限性。Parikh等[22]认为,CHA_2DS_2-VASc能对$CHADS_2$评分低危患者进行更细化的脑卒中风险分层。Olesen等[15]指出,$CHADS_2$评分为零,同时CHA_2DS_2-VASc评分亦为零,心房颤动相关性缺血性卒中的风险方为低危人群。因此,将$CHADS_2$评分与CHA_2DS_2-VASc评分相结合,能够更准确地评价缺血性卒中发生风险。

四、预防性治疗

心房颤动相关性缺血性卒中预防性治疗意义重大,可有效改善患者预后。Honma[23]对743例伴非瓣膜性心房颤动的急性脑血管病(包括缺血性卒中和短暂性脑缺血发作)患者进行分组和对照研究,其结果显示,与发病前确定有心房颤动的缺血性卒中患者相比,发病前未确定有心房颤动的缺血性卒中患者行抗凝治疗的比例显著减少,且临床转归良好率显著降低(出院时为41%对51%、随访3个月时为46%对56%)。提示唯有及早发现并对其及时采取相应处理措施,才能最大程度改善预后。

心房颤动相关性卒中的预防性治疗包括控制危险因素、心房颤动消除术、药物治疗。心房颤动消除术是最彻底的治疗措施,但术后极易复发。药物治疗是最基本的预防性治疗,分为抗血小板治疗和抗凝治疗,能够显著降低心房颤动相关性缺血性卒中发生率[24]。

1.药物治疗原则 根据评价体系判断缺血性卒中风险高低及不良反应(脑出血)决定是否用药;根据不同药物治疗作用和不良反应选择药物种类。2012年美国胸科学会(ATS)指南推荐[25]:$CHADS_2$评分为零者,予抗血小板治疗或不治疗;$CHADS_2$评分1分者,予抗血小板治疗或抗凝治疗;$CHADS_2$评分≥2分者,予抗凝治疗。2010年欧洲心脏病学会(ESC)管理指南推荐[1]:$CHADS_2$评分≥2分者,予

抗凝治疗；$CHADS_2$评分1分者，予抗凝治疗；$CHADS_2$评分为零且CHA_2DS_2-VASc评分也为零者，行抗凝与抗血小板联合治疗；$CHADS_2$评分为零且CHA_2DS_2-VASc评分为1分者，予抗凝治疗或抗血小板治疗，首选抗凝治疗；$CHADS_2$评分为零且CHA_2DS_2-VASc评分≥2分，予抗凝治疗。2010年美国心脏协会/美国卒中协会指南推荐$CHADS_2$评分1分者予抗凝治疗，但不推荐以双联抗血小板治疗替代华法林抗凝治疗[14]。HAS-BLED评价体系是最简单可靠的抗凝治疗出血风险评价体系，包括高血压、肝功能异常、肾功能异常、脑卒中、出血史、国际标准化比值（INR）不稳定、年龄>65岁、联合用药和饮酒共9项内容，每项1分，总评分为9分，评分越高，出血风险越大[26]；其中评分≥3分者属于出血高危人群，除非脑卒中风险很高，否则不宜行抗凝治疗。目前已达成共识：<65岁且无心房颤动相关性缺血性卒中危险因素的非瓣膜性心房颤动患者，予阿司匹林300～350 mg/d；≥65岁且有基础疾病或心房颤动相关性缺血性危险因素的非瓣膜性心房颤动，予华法林治疗[6]。

2. 抗血小板治疗　Varughese和Halperin[27]指出，抗血小板治疗对心房颤动相关性缺血性卒中的预防效果不及抗凝治疗。阿哌沙班是一种新型抗凝药物，阿哌沙班与阿司匹林预防维生素K拮抗剂无效或不合适心房颤动患者脑卒中比较研究（AVERROES）结果显示，阿哌沙班组患者脑卒中或全身性栓塞年发生率为1.60%、阿司匹林组为3.70%[28]。因此，阿司匹林不适用于脑卒中风险高的患者，而且长期应用阿司匹林可产生诸如消化道出血等并发症[29]。阿哌沙班减少心房颤动相关性卒中及其他栓塞事件（ARISTOTLE）研究表明，阿哌沙班组患者严重出血年发生率为2.13%、华法林组为3.09%[25]。AVERROES研究结果显示，阿哌沙班组严重出血年发生率为1.40%、阿司匹林组为1.20%[30]。上述两项研究表明，新型抗凝药出血发生率低于传统抗凝药，阿司匹林出血发生率又低于新型抗凝药。Flaker和Weachter[31]的研究发现，阿司匹林的疗效并不随药物剂量的增加而提高，而不良反应则随着药物剂量的增加而提高，因此，必须控制阿司匹林的剂量。AVERROES研究应用的阿司匹林剂量为81～324 mg（1次/d）[27]。

3. 抗凝治疗　抗凝治疗是心房颤动相关性缺血性卒中的主要预防性治疗。抗凝药物既包括华法林等传统药物，又包括达比加群等新型药物。近年来，应用NOACs进行心房颤动相关性卒中和栓塞性疾病预防性治疗的研究取得了突破性进展，并取得专家共识和形成相关指南[12]。（1）传统抗凝药：Hickey[32]认为，华法林可使心房颤动相关性缺血性卒中风险降低2/3；Komatsu等[5]研究发现，华法林组患者心房颤动相关性缺血性卒中年发生率为0.88%。凝血因子Xa（FXa）抑制剂利伐沙班每日一次口服与维生素K拮抗剂预防心房颤动性缺血性卒中和栓塞比较试验（ROCKET-AF）显示，华法林组患者脑卒中和栓塞事件发生率为2.16%[33]。ARISTOTLE研究结果显示，华法林组患者脑卒中和栓塞事件发生率为1.60%[30]。长期抗凝治疗随机评价（RE-LY）试验结果显示，华法林组患者脑卒中和栓塞事件发生率为1.71%[34]。Diener等[35]对RE-LY试验的资料进行分析，发现有脑卒中或短暂性脑缺血发作病史的患者（1195例）脑卒中和动脉系统栓塞年发生率为2.78%，但华法林可增加出血风险，需定期监测国际标准化比值。Riva等[36]认为，较高的出血发生率、治疗时间窗狭窄、疗效易受食物和药物影响等因素，使华法林的临床应用受到很大限制。Mazzaglia等[37]指出，华法林治疗相关性出血与增龄具有关联性，因此，对年龄较大的心房颤动患者应避免行抗凝治疗。虽然华法林有上述不足，但目前仍是心房颤动相关性缺血性卒中预防治疗的主要药物。（2）NOACs：NOACs按照作用原理分为直接凝血酶抑制剂和凝血因子Xa抑制剂，前者有达比加群、西美加群，后者有利伐沙班、阿哌沙班、伊多沙班。NOACs以其更强的脑卒中预防效果和更高的安全性受到广泛关注。Klein[38]的研究显示，与华法林和阿司匹林相比，服用阿哌沙班的患者脑卒中和全身性栓塞发生率较低，且出血率也较低。Miller等[39]进行的一项Meta分析显示，NOACs不但预防脑卒中的疗效优于华法林，其颅内出血风险也低于华法林，而且具有服用方便、不必定期检测之优点。Mearns[40]认为，新型抗凝药可以每日定量服用、不必定期检测、预防效果稳定且较少受到其他因素的影响，是一种较为理想的抗凝药物。Jiménez等[41]认为，阿哌沙班不仅抗凝作用安全、有效，而且疗效稳定、服用剂量固定，因此Watson等[42]认为新型抗凝药可能成为更加安全有效的预防心房颤动相关性缺血性卒中的药物。Mga[43]甚至提出，新型抗凝药的出现标志着心房颤动相关性缺血性卒中

预防与治疗新时代的到来。达比加群在2011年被美国心脏协会推荐作为心房颤动相关性缺血性卒中的预防用药[44]。Alexander等[45]的研究显示，阿哌沙班联合抗血小板药物可增加严重出血风险，因此，二者不宜联合应用。Armaganijan等[46]认为，新型抗凝药仍待多中心大样本随机对照临床试验以验证其安全性和有效性，目前尚不宜在临床大量推广应用。(3)抗凝药和抗炎药联合应用：Obata等[47]研究发现，华法林与布可隆联合应用可增加华法林的抗凝作用，从而减少华法林的剂量。

五、小结与展望

心房颤动是临床最为常见的心律失常，也是缺血性卒中和心功能损害的主要原因[48]，因此，应该引起脑血管病医务工作者的高度注意，将其列入重要研究课题。对心房颤动的研究应分为两方面：一方面应加强对心房颤动的基础研究，即寻找发病原因；另一方面应加强对心房颤动的临床研究，阐明心房颤动相关性缺血性卒中的发生规律和有效的预防与治疗方法。目前，心房颤动的基础与临床研究均已取得一定进展：微小RNA(miRNA)与心房颤动的相关性研究正受到广泛关注，有研究表明，miRNA参与对心房颤动相关基因的调控[49]；针对心房颤动相关性缺血性卒中发生率、危险因素进行的一系列研究，初步建立了临床评价体系，制定了有针对性的治疗体系，例如，何种情况行抗血小板治疗，何种情况行抗凝治疗等，但仍有许多问题尚待解决。新型抗凝药物的出现，为心房颤动相关性缺血性卒中的治疗带来了希望，也带来了挑战。相信未来在科技发展的推动下，心房颤动的基础与临床研究必会取得突破性进展，使心房颤动相关性缺血性卒中的发生率大幅下降。

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·小词典·

中英文对照名词词汇（三）

22个国家缺血性和出血性卒中危险因素病例对照研究
Risk Factors for Ischemic and Intracerebral Hemorrhagic Stroke in 22 Countries（INTERSTROKE）study

骨保护素 osteoprotegerin（OPG）

国际动脉粥样硬化学会
International Atherosclerosis Society（IAS）

国际糖尿病联盟 International Diabetes Federation（IDF）

国际头痛疾病分类第2版
International Classification of Headache Disorders Second Edition（ICHD-Ⅱ）

红细胞沉降率 erythrocyte sedimentation rate（ESR）

环氧合酶 cyclooxygenase（COX）

黄体生成素 luteinizing hormone（LH）

活化部分凝血活酶时间
activated partial thromboplastin time（APTT）

霍奇金淋巴瘤 Hodgkin's lymphoma（HL）

急性脑出血强化降压试验
Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial（INTERACT）

脊髓小脑共济失调 spinocerebellar ataxia（SCA）

家庭血压监测 home blood pressure monitoring（HBPM）

简易智能状态检查量表
Mini-Mental State Examination（MMSE）

降压治疗试验协作组
Blood Pressure Lowering Treatment Trialists' Collaboration（BPLTTC）

胶质纤维酸性蛋白 glial fibrillary acidic protein（GFAP）

焦虑自评量表 Self-Rating Anxiety Scale（SAS）

经颅多普勒超声 transcranial Doppler ultrasound（TCD）

颈动脉内膜切除术 carotid endarterectomy（CEA）

颈动脉支架成形术 carotid artery stenting（CAS）

静脉注射免疫球蛋白 intravenous immunoglobulin（IVIg）

巨噬细胞清道夫受体1
macrophage scavenger receptor 1（MSR1）

抗核抗体 anti-nuclear antibody（ANA）

抗磷脂抗体综合征
anti-phospholipid antibody syndrome（APS）

抗心磷脂抗体 anti-cardiolipin antibody（ACA）

抗中性粒细胞胞质抗体
anti-neutrophil cytoplasmic antibody（ANCA）

颗粒增强免疫比浊法
particle-enhanced turbidimetric immunoassay（PETIA）