

文章编号:1003-2754(2024)03-0280-04

doi:10.19845/j.cnki.zfysjbbzz.2024.0055



不明原因栓塞性卒中

迟冬雨^{1,2,3}综述, 宋秀娟^{1,2,3}审校

摘要: 不明原因栓塞性卒中(ESUS)目前被认为是在影像上表现为栓塞性卒中,且经仔细诊断评估后,未确定特定的或公认的卒中病因的隐源性卒中亚型。据推测,在ESUS患者卒中二级预防中,抗凝治疗比抗血小板治疗更有效。然而,实际上在几项相关ESUS实验中,抗凝治疗相比于阿司匹林既不安全,也不有效。故更确切地理解和判断ESUS的病因是治疗的关键。本文将讨论ESUS概念的背景、定义、诊断,从栓子来源分析其病因及与ESUS的关联,以期提高临床医生的认识。

关键词: 不明原因栓塞性卒中; 非狭窄性大动脉粥样硬化; 亚临床房颤; 卵圆孔未闭

中图分类号: R743.3 **文献标识码:** A

Embollic stroke of undetermined source CHI Dongyu, SONG Xiujuan. (Department of Neurology of The Second Hospital of Hebei Medical University, Hebei Provincial Key Laboratory of Neurology, Ministry of Education Key Laboratory of Clinical Neurology, Shijiazhuang 050000, China)

Abstract: Embollic stroke of undetermined source (ESUS) is currently considered to be a subtype of cryptogenic stroke featuring embolic stroke on imaging but with no specific or recognized cause of stroke identified after careful diagnostic evaluation. It was speculated that anticoagulant therapy was more effective than antiplatelet therapy for secondary prevention of stroke in patients with ESUS. However, in fact, several ESUS trials showed that anticoagulant therapy was neither safer nor more effective compared with aspirin. Therefore, a more accurate understanding and determination of the etiology of ESUS is the key to treatment. In this paper, we discuss the background, definition, and diagnosis of ESUS, and analyze its etiology and the relationship between emboli and ESUS from the perspective of embolus source, with the aim to improve clinicians' understanding of ESUS.

Key words: Embollic stroke of undetermined source; Nonstenotic large-artery atherosclerosis; Subclinical atrial fibrillation; Patent foramen ovale

全世界每年约有1 370万人发生卒中,这使其成为全球第二大致死原因和长期致残的主要原因,其中80%以上是缺血性卒中^[1]。缺血性卒中可由多种原因引起,根据TOAST分型,其病因主要分为:大动脉粥样硬化型、心源性栓塞、小动脉闭塞、其他明确病因及未确定病因的卒中^[2]。约有1/3的缺血性卒中经过标准评估后没有找到病因,这种卒中被定义为隐源性卒中(cryptogenic stroke, CS)^[3]。由于隐源性卒中的临床和神经影像特征通常提示是远处的栓塞源,而不是原位的脑小血管闭塞,故而,于2014年提出了不明原因栓塞性卒中(embolic strokes of undetermined source, ESUS)的概念^[4]。ESUS占缺血性卒中的17%^[5],潜在的栓子来源包括动脉、心脏与静脉等。本文主要讨论不同类型栓子来源与ESUS的关联,分析其机制、临床特征等,以期能提高临床医生对其的认识,及早发现卒中的病因,并进行正确的防治工作。

1 CS与ESUS的概念

隐源性卒中(CS)是一种病因尚不明确的缺血性卒中亚型,约占所有缺血性卒中的1/3左右^[3]。根据TOAST分型^[2]标准,CS包括没有明确机制的卒中、存在一个以上潜在机制的卒中,以及相关检查不完全

的卒中。因此,CS中包含其他不同类型的卒中患者。为了方便临床,2014年,Hart等^[4]提出,大多数隐源性卒中是栓塞性的,其栓子可以来自二尖瓣、主动脉瓣或左心腔(心源性栓塞),来自大脑近端动脉或主动脉弓(动脉源性栓塞),也可以来自静脉(反常栓塞)。基于此,引入了不明原因栓塞性卒中(ESUS)的概念。ESUS是指在头部CT或MRI上有栓塞性或非腔隙性脑梗死的急性缺血性卒中,而不伴有同侧颅外或颅内血管狭窄>50%,或没有与急性缺血性卒中的主要风险相关的可识别的心源性栓塞源,如房颤或左心室血栓等^[4]。大多数有隐源性卒中的患者都符合这一定义。

2 ESUS临床特征和诊断

根据隐源性卒中/ESUS国际工作组提出的标准,ESUS被定义为在没有下列情况下的非腔隙性脑

收稿日期:2023-05-10;修订日期:2023-10-20

基金项目:河北省医学科学研究课题(20211276)

作者单位:(1. 河北医科大学第二医院神经内科,河北石家庄050000;2. 河北省神经病学重点实验室,河北石家庄050000;3. 临床神经病学教育部重点实验室,河北石家庄050000)

通信作者:宋秀娟,E-mail:songxiujuan1@126.com

梗死^[4]:(1)颅外或颅内动脉硬化导致缺血区动脉管腔狭窄 $\geq 50\%$;(2)主要或危险的心脏栓塞源,以及(3)任何其他少见的卒中原因(如大动脉炎、夹层、偏头痛/血管痉挛、药物滥用等)。因此,脑部计算机断层扫描(CT)或磁共振成像(MRI)、12导联心电图、超声心动图、24 h或更长时间的心电监测,以及颅内外动脉血管成像等检查,对于诊断ESUS至关重要。

从影像学上^[6],ESUS更类似于心源性或主动脉弓源的栓塞,可能同时累及左、右双侧或前、后循环。但与单纯心源性栓塞不同的是,ESUS的病灶可能较小。因此,ESUS患者临床神经功能损害程度低于心源性栓塞,预后更好^[7-9]。ESUS后卒中复发的平均风险约为每年4.5%^[5]。此外,与非ESUS缺血性卒中患者相比,ESUS患者更年轻,更少受到传统心血管危险因素的影响^[5,7,10]。

ESUS患者除了临床上症状性卒中中的高发生率外,所谓的无症状缺血性损害(silent ischemic lesions, SILs)的发生率甚至更高。SILs可以通过脑成像,即计算机断层扫描,或者磁共振成像(MRI)来检测。在隐源性卒中后90 d,14.5%的患者报告了新的SILs^[11]。SILs是卒中复发的独立危险因素^[12]。

3 不同病因的ESUS

脑栓塞的栓子来源是ESUS的基础。栓子根据其来源的不同可主要分为:来源于供血动脉的栓子、心脏本身的栓子以及外周静脉循环的栓子。一项对800名接受连续ESUS治疗患者的大型多中心数据集的相关性分析表明,颈部或脑血管的非狭窄性大动脉疾病、PFO和房颤等病因,分别占患者的48.5%、21.3%和15.0%^[13]。不同栓子的来源不同,其致病机制也相对不同。

3.1 来源于供血动脉的栓子 动脉-动脉的栓塞是缺血性卒中常见的病因。栓子主要源于动脉粥样硬化斑块的破裂或者继发血栓的脱落。目前的卒中分类系统大多认为 $\geq 50\%$ 的管腔狭窄才能诱发大动脉疾病^[2]。一些病例可能是大脑循环中的非狭窄性大动脉粥样硬化斑块脱落引起的动脉至动脉的栓塞,由于它们不会导致动脉管腔的明显狭窄,因此无法识别。随着时代的进展,先进的成像方法的出现使得越来越多的易损斑块的证据被发现,这也意味着非狭窄性大动脉粥样硬化与ESUS的因果关系得以被进一步发现和证实。斑块内出血、富含脂质的坏死核、斑块新生血管、斑块厚度、斑块体积和表面形态等可能揭示了动脉粥样硬化的高危特征^[14,15]。

越来越多的证据表明,来源于供血动脉的非狭窄性大动脉粥样硬化的作用比最初认为的更大。在对Navise-ESUS试验的探索性分析中,颈动脉斑块在确诊的缺血性卒中的同侧比对侧更常见(65%8%)^[16]。

在同一分析中,颈动脉狭窄在确诊的缺血性卒中的同侧比对侧更常见(51%17%)^[16]。一项相关研究的荟萃分析证实了这些结果,该分析显示,在同侧和对侧颈动脉发现具有高风险特征的斑块的优势比为5.5(95%CI 2.5~12.0)^[17]。此外,有研究发现,超声检测到的非狭窄颈动脉斑块的存在与ESUS患者卵圆孔未闭呈负相关,提示非狭窄性颈动脉斑块在ESUS中的独立作用^[18,19]。越来越多的证据表明,非狭窄性颈动脉斑块在ESUS患者中同侧比对侧更常见,这支持了非狭窄性动脉粥样硬化在ESUS中的重要病因作用。

3.2 来源于心脏本身的栓子 在ESUS最开始被提出时,认为房颤可能是这一隐源性卒中亚型中的主要原因。房颤是常见的心律失常类型,可以表现为永久性、持续性和阵发性。目前认为房颤相关卒中的主要机制:心房无序地颤动,使得心脏收缩功能障碍,心房血流无法完全被放出而淤滞在心房内,易导致心房附壁血栓的形成,附壁血栓脱落形成的栓子随血流进入脑血管引发脑卒中^[20]。随着现代植入式起搏器、除颤器和心脏监测器的问世,这些设备可以对房性心律失常进行高敏感度、长期、持续的监测,即使这些心律失常是无症状的并且非常短暂^[21,23]。通过长期持续监测,大约1/3的人可以检测到持续几分钟到几小时(一般认为 >6 min, <24 h)的无症状心房颤动,这被称为亚临床房颤^[21,22]。

大型队列研究表明,房颤患者卒中的风险增加了4~5倍^[24,25]。一项对只接受抗血小板治疗的房颤患者的分析表明,在校正了其他临床卒中危险因素后,永久性房颤患者卒中的风险明显更高,其次是持续性房颤患者,然后是阵发性房颤患者^[26]。即使是没有临床表现的亚临床房颤也与卒中风险增加2.5倍相关^[27]。ASSET研究招募了2 580例最近植入起搏器或除颤器、至少有1个卒中危险因素、没有房颤病史的患者。在平均2.5年的随访期内,在植入装置后的前3个月内,单次房颤发作持续 ≥ 6 min的患者发生卒中的风险增加了2.5倍^[27]。

然而,在房颤实验模型中看到的结构重构发生在至少1周的持续快速起搏之后^[28],因此,房颤引起的任何心房变化不太可能解释单次6 min的房颤发作与卒中风险增加之间的联系。房颤可能不是导致心房血栓栓塞的唯一原因。房颤常发生在心房异常的环境中,如内皮功能障碍^[29]、纤维化^[30]、心肌细胞功能受损^[31]、心腔扩张^[32]、左心耳机械功能障碍^[33]等。有研究发现,心房功能障碍的标志物与隐源性或栓塞性卒中有关,而与原发脑小血管闭塞无关,表明这些标志物是心房血栓栓塞的特定风险信号,而不是一般血管风险信号^[34,35]。钠尿肽前体

A基因的纯合子突变时,即使没有房颤,这种疾病也会导致心房扩张、心房活动进行性丧失,最终导致心房停顿和血栓栓塞症^[36]。这些发现提示,不合并房颤的房性心脏病可能是ESUS的一种潜在致病机制,需要引起重视。

3.3 来源于外周静脉循环的栓子 来自静脉的栓子在患者存在心内分流或者肺水平分流等情况时,可以从静脉循环进入动脉循环,当这类栓子进入脑血管可导致脑栓塞。这种栓塞机制被称为反常栓塞^[37]。卵圆孔未闭(patent foramen ovale, PFO)是最常见的胎源性先天性心脏病,在普通成年人群中的患病率约为25%,在ESUS人群中患病率高达40%^[38,39]。3项RCT试验报告称,在ESUS患者中,经导管封堵PFO与药物治疗相比,卒中的复发率显著减少^[40]。这些针对PFO治疗的获益支持了一直以来的假说,即PFO可能是卒中的致病机制。反常栓塞被认为是PFO引起脑卒中的主要机制^[41]。

由于PFO患病率较高,当ESUS合并PFO时,需对其因果关系进行全面的判断和分析。Kent等^[42]使用反常性栓塞风险量表(Risk of Paradoxical Embolism, RoPE)评分来识别PFO的存在是致病性的还是偶发性的。一般认为RoPE评分0~3分,几乎不考虑PFO为卒中病因,RoPE评分>6分认为其是PFO相关卒中^[43]。此外,有研究显示,具有高危解剖结构特征的PFO如:长隧道PFO、房间隔过度活动、咽鼓管瓣或Chiari's网、Valsalva动作时RLS较大、下腔静脉(IVC)和PFO之间夹角较小等,与CS有独立相关性^[44]。2021年《卵圆孔未闭相关卒中预防中国专家指南》提出了PFO相关卒中筛查的关键点包括:年龄<55岁、CT/MRI显示多发缺血性病灶高危PFO、临床栓塞事件复发、DVT/PE病史或易栓症、Valsalva动作相关血栓栓塞事件、呼吸睡眠暂停、长途旅行/静止状态下相关临床事件、同时发生体循环/肺循环栓、RoPE评分>6分者等,以确定哪些卒中与PFO有因果关系,评估PFO患者适宜的“个体化”治疗^[45]。

3.4 其他 除了心脏病及动脉疾病以外,全身性疾病也受到重视。如癌症患者的卒中风险显著增加,这种风险因癌症分期和类型而异(例如,肺癌患者的风险最大)^[46]。癌症与卒中的联系是由多种病理因素引起的,如高凝血症、肿瘤栓塞、血管机械性压迫、肉芽肿性心内膜炎、贫血、放射治疗、抗肿瘤治疗的不良反应和其他^[47]。此外,其他疾病包括偏头痛、遗传基因突变、自身免疫和风湿性疾病、血栓前状态和高凝状态等,都可能是ESUS的潜在病因^[48]。

4 结论与展望

ESUS是一种特殊的卒中亚型,其包含了多种不同的潜在栓塞源,包括非狭窄性动脉粥样硬化、未发现的阵发性房颤、房性心脏病、PFO以及其他相关病

因。不同栓子来源不同,致病机制不同,其治疗方案也相对不同。ESUS最佳二级预防仍然不明,来自随机对照试验的现有证据表明,抗凝治疗(使用VKA或NOAC)相比于阿司匹林既不有效,也不安全^[7,49]。对于ESUS患者需要进行彻底的检查,比现行ESUS诊断标准要求更全面的诊断检查,包括高分辨率血管成像、TEE和至少48 h Holter监测等,可能有助于临床医生发现ESUS患者脑血栓的来源,并使治疗方法个体化,降低卒中负担。

利益冲突声明: 所有作者均声明不存在利益冲突。

作者贡献声明: 迟冬雨、宋秀娟负责设计论文框架、起草论文;迟冬雨负责论文修改;宋秀娟负责拟定写作思路、指导撰写论文并最后定稿。

[参考文献]

- [1] 2016 Stroke Collaborators GBD. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016 [J]. *Lancet Neurol*, 2019, 18(5): 439-458.
- [2] Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment [J]. *Stroke*, 1993, 24(1): 35-41.
- [3] Ornello R, Degan D, Tiseo C, et al. Distribution and temporal trends from 1993 to 2015 of ischemic stroke subtypes: a systematic review and meta-analysis [J]. *Stroke*, 2018, 49(4): 814-819.
- [4] Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct [J]. *Lancet Neurol*, 2014, 13(4): 429-438.
- [5] Hart RG, Catanese L, Perera KS, et al. Embolic stroke of undetermined source: a systematic review and clinical update [J]. *Stroke*, 2017, 48(4): 867-872.
- [6] Wang W, Tang X, Liu W, et al. Clinical features of embolic stroke of undetermined source [J]. *Front Neurol*, 2020, 11: 58.
- [7] Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source [J]. *N Engl J Med*, 2018, 378(23): 2191-2201.
- [8] Ntaios G, Papavasileiou V, Milonis H, et al. Embolic strokes of undetermined source in the Athens stroke registry: an outcome analysis [J]. *Stroke*, 2015, 46(8): 2087-2093.
- [9] Toyoda K, Okumura K, Hashimoto Y, et al. Identification of covert atrial fibrillation in cryptogenic ischemic stroke: current clinical practice in Japan [J]. *J Stroke Cerebrovasc Dis*, 2016, 25(8): 1829-1837.
- [10] Martinez-Majander N, Aarnio K, Pirinen J, et al. Embolic strokes of undetermined source in young adults: baseline characteristics and long-term outcome [J]. *Eur J Neurol*, 2018, 25(3): 535-541.
- [11] Bal S, Patel SK, Almekhlafi M, et al. High rate of magnetic resonance imaging stroke recurrence in cryptogenic transient ischemic attack and minor stroke patients [J]. *Stroke*, 2012, 43(12): 3387-3388.
- [12] Gioia LC, Tollard É, Dubuc V, et al. Silent ischemic lesions in young adults with first stroke are associated with recurrent stroke [J]. *Neurology*, 2012, 79(12): 1208-1214.
- [13] Ntaios G, Perlepe K, Lambrou D, et al. Prevalence and overlap of potential embolic sources in patients with embolic stroke of undetermined source [J]. *J Am Heart Assoc*, 2019, 8(15): e012858.
- [14] Mujaj B, Bos D, Muka T, et al. Antithrombotic treatment is asso-

- ciated with intraplaque haemorrhage in the atherosclerotic carotid artery: a cross-sectional analysis of The Rotterdam Study [J]. *Eur Heart J*, 2018, 39(36):3369-3376.
- [15] Saba L, Saam T, Jäger HR, et al. Imaging biomarkers of vulnerable carotid plaques for stroke risk prediction and their potential clinical implications[J]. *Lancet Neurol*, 2019, 18(6):559-572.
- [16] Ntaios G, Swaminathan B, Berkowitz SD, et al. Efficacy and safety of rivaroxaban versus aspirin in embolic stroke of undetermined source and carotid atherosclerosis[J]. *Stroke*, 2019, 50(9):2477-2485.
- [17] Kamtchum-Tatuene J, Wilman A, Saqqur M, et al. Carotid plaque with high-risk features in embolic stroke of undetermined source: systematic review and meta-analysis [J]. *Stroke*, 2020, 51(1):311-314.
- [18] Jaffre A, Guidolin B, Ruidavets JB, et al. Non-obstructive carotid atherosclerosis and patent foramen ovale in young adults with cryptogenic stroke[J]. *Eur J Neurol*, 2017, 24(5):663-666.
- [19] Ntaios G, Sagris D, Strambo D, et al. Carotid atherosclerosis and patent foramen ovale in embolic stroke of undetermined source[J]. *J Stroke Cerebrovasc Dis*, 2021, 30(1):105409.
- [20] Zimetbaum P, Waks JW, Ellis ER, et al. Role of atrial fibrillation burden in assessing thromboembolic risk [J]. *Circ Arrhythm Electrophysiol*, 2014, 7(6):1223-1229.
- [21] Younis A, Heist EK, McNitt S, et al. Predictors and outcomes of atrial tachyarrhythmia among patients with implantable defibrillators[J]. *Heart Rhythm*, 2020, 17(4):553-559.
- [22] Gorennek B, Bax J, Boriani G, et al. Device-detected subclinical atrial tachyarrhythmias: definition, implications and management-an European Heart Rhythm Association (EHRA) consensus document, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE) [J]. *Europace*, 2017, 19(9):1556-1578.
- [23] Ziegler PD, Rogers JD, Ferreira SW, et al. Long-term detection of atrial fibrillation with insertable cardiac monitors in a real-world cryptogenic stroke population[J]. *Int J Cardiol*, 2017, 244:175-179.
- [24] Migdady I, Russman A, Buletko AB. Atrial fibrillation and ischemic stroke: a clinical review [C]. *Seminars in Neurology*, 2021, 41(4):348-364.
- [25] Escudero-Martinez I, Morales-Caba L, Segura T. Atrial fibrillation and stroke: a review and new insights[J]. *Trends in Cardiovascular Medicine*, 2023, 33(1):23-29.
- [26] Vanassche T, Lauw MN, Eikelboom JW, et al. Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES [J]. *Eur Heart J*, 2015, 36(5):281-288.
- [27] Healey JS, Lopes RD, Granger CB, et al. Apixaban for stroke prevention in subclinical atrial fibrillation [J]. *New England Journal of Medicine*, 2024, 390(2):107-117.
- [28] De Jong AM, Maass AH, Oberdorf-Maass SU, et al. Mechanisms of atrial structural changes caused by stretch occurring before and during early atrial fibrillation [J]. *Cardiovasc Res*, 2011, 89(4):754-765.
- [29] Corban MT, Toya T, Ahmad A, et al. Atrial fibrillation and endothelial dysfunction: a potential link? [C]. *Elsevier*, 2021, 96(6):1609-1621.
- [30] Miyauchi S, Tokuyama T, Takahashi S, et al. Relationship between fibrosis, endocardial endothelial damage, and thrombosis of left atrial appendage in atrial fibrillation [J]. *JACC. Clinical electrophysiology*, 2023, 9(7 Pt2):1158-1168.
- [31] Wiersma M, Marion DMS, Wüst RCI, et al. Mitochondrial dysfunction underlies cardiomyocyte remodeling in experimental and clinical atrial fibrillation [J]. *Cells*, 2019, 8(10):1202.
- [32] Ortiz-Leon XA, Posada-Martinez EL, Trejo-Paredes MC, et al. Tricuspid and mitral remodelling in atrial fibrillation: a three-dimensional echocardiographic study [J]. *European Heart Journal-Cardiovascular Imaging*, 2022, 23(7):944-955.
- [33] Mao Y, Yu C, Yang Y, et al. Comparison of left atrial and left atrial appendage mechanics in the risk stratification of stroke in patients with atrial fibrillation [J]. *Cardiovascular Ultrasound*, 2021, 19:1-12.
- [34] Kamel H, Hunter M, Moon YP, et al. Electrocardiographic left atrial abnormality and risk of stroke: northern Manhattan study [J]. *Stroke*, 2015, 46(11):3208-3212.
- [35] Kamel H, O'Neal WT, Okin PM, et al. Electrocardiographic left atrial abnormality and stroke subtype in the atherosclerosis risk in communities study [J]. *Ann Neurol*, 2015, 78(5):670-678.
- [36] Disertori M, Quintarelli S, Grasso M, et al. Autosomal recessive atrial dilated cardiomyopathy with standstill evolution associated with mutation of Natriuretic Peptide Precursor A [J]. *Circ Cardiovasc Genet*, 2013, 6(1):27-36.
- [37] Jolobe O. Wide-ranging clinical spectrum of paradoxical embolism [J]. *Postgraduate Medical Journal*, 2022, 98(1166):958-966.
- [38] Mojaddidi MK, Zaman MO, Elgendy IY, et al. Cryptogenic stroke and patent foramen ovale [J]. *J Am Coll Cardiol*, 2018, 71(9):1035-1043.
- [39] Teshome MK, Najib K, Nwagbara CC, et al. Patent foramen ovale: a comprehensive review [J]. *Curr Probl Cardiol*, 2020, 45(2):100392.
- [40] Mas JL, Derumeaux G, Guillon B, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke [J]. *N Engl J Med*, 2017, 377(11):1011-1021.
- [41] Lucà F, Pino P G, Parrini I, et al. Patent foramen ovale and cryptogenic stroke: integrated management [J]. *Journal of Clinical Medicine*, 2023, 12(5):1952.
- [42] Kent DM, Saver JL, Ruthazer R, et al. Risk of paradoxical embolism (RoPE)-estimated attributable fraction correlates with the benefit of patent foramen ovale closure [J]. *Stroke*, 2020, 51(10):3119-3123.
- [43] Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke [J]. *Neurology*, 2013, 81(7):619-625.
- [44] Nakayama R, Takaya Y, Akagi T, et al. Identification of high-risk patent foramen ovale associated with cryptogenic stroke: development of a scoring system [J]. *J Am Soc Echocardiogr*, 2019, 32(7):811-816.
- [45] 张玉顺, 蒋世良, 朱鲜阳. 卵圆孔未闭相关卒中预防中国专家指南 [J]. *心脏杂志*, 2021, 33(1):1-10.
- [46] Navi BB, Reiner AS, Kamel H, et al. Risk of arterial thromboembolism in patients with cancer [J]. *J Am Coll Cardiol*, 2017, 70(8):926-938.
- [47] Navi BB, Iadecola C. Ischemic stroke in cancer patients: a review of an underappreciated pathology [J]. *Ann Neurol*, 2018, 83(5):873-883.
- [48] Schulz UG. Cryptogenic stroke-How to make sense of a non-diagnostic entity [J]. *Maturitas*, 2019, 122:44-50.
- [49] Diener HC, Sacco RL, Easton JD, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source [J]. *N Engl J Med*, 2019, 380(20):1906-1917.

引证本文:迟冬雨,宋秀娟.不明原因栓塞性卒中[J].中馈与神经疾病杂志,2024,41(3):280-283.